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WO 02/099388 A2

(54) Title: BENZODIAZEPINE BRADYKININ ANTAGONISTS

(57) Abstract: Compounds disclosed here or a pharmaceutically acceptable salt thereof, are bradykinin B1 antagonist compounds useful in the treatment or prevention of symptoms such as pain and inflammation associated with the bradykinin B1 pathway.

TITLE OF THE INVENTION
BENZODIAZEPINE BRADYKININ ANTAGONISTS

BACKGROUND OF THE INVENTION

This invention is directed to benzodiazepine compounds. In particular, this invention is directed to benzodiazepine compounds that are bradykinin B1 antagonists or inverse agonists having selectivity against the bradykinin B2 receptor.

Bradykinin ("BK") is a kinin that plays an important role in the pathophysiological processes accompanying acute and chronic pain and inflammation. Bradykinins, like other related kinins, are autocoid peptides produced by the catalytic action of kallikrein enzymes on plasma and tissue precursors termed kininogens. Inhibition of bradykinin B1 receptors by compounds that are bradykinin B1 antagonists or inverse agonists would provide relief from maladies that mediate undesirable symptoms through a BK B1 receptor pathway. Accordingly, there is a need for novel compounds that are effective bradykinin B1 antagonists or inverse agonists.

U.S. Patent Nos. 5,220,018, 5,302,591, 5,360,802, 5,451,582, 5,478,933, 5,521,175, 5,556,969, 5,696,110, and 5,728,829 describe compounds that are cholecystokinin ("CCK") and gastrin antagonists. European Patent Nos. EP 434364, EP 514133, and EP 538945 describe compounds that are CCK and gastrin antagonists. British Patent No. GB 2271354 describes compounds that are CCK and gastrin antagonists. International Patent Publication Nos. WO 9302078, WO 9307131, WO 9319052, WO 9400438, WO 9403437, WO 9403447, WO 9506041, and WO 9815535 describe compounds that are CCK and gastrin antagonists.

G. Semple et al., *J. Med. Chem.*, 40:331-341(1997), M. Satoh et al., *Chem. Pharm. Bull.*, 44:1412-1414(1996) describe compounds that are CCK and gastrin antagonists. M.G. Bock and J. Longmore, *Current Opinion in Chem. Biol.*, 4:401-406(2000) describes bradykinin antagonists.

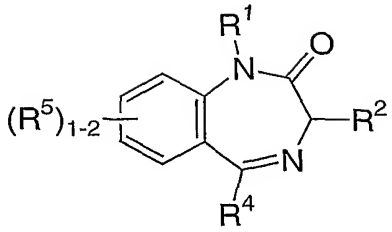
Nevertheless, there remains a need for new effective bradykinin B1 antagonists to treat chronic pain and inflammation. Such compounds would be effective in the treatment or prevention of pain including, for example, bone and joint pain (osteoarthritis), repetitive motion pain, dental pain, cancer pain, myofascial pain (muscular injury, fibromyalgia), perioperative pain (general surgery, gynecological) and chronic pain. In particular, inflammatory pain such as, for example, inflammatory

airways disease (chronic obstructive pulmonary disease) would be effectively treated by bradykinin B1 antagonist compounds.

Further, such compounds may additionally be used to treat asthma, inflammatory bowel disease, rhinitis, pancreatitis, cystitis (interstitial cystitis), uveitis, inflammatory skin disorders, rheumatoid arthritis and edema resulting from trauma associated with burns, sprains or fracture. They may be used subsequent to surgical intervention (e.g. as post-operative analgesics) and to treat inflammatory pain of varied origins (e.g. osteoarthritis, rheumatoid arthritis, rheumatic disease, teno-synovitis and gout) as well as for the treatment of pain associated with angina, menstruation or cancer. They may be used to treat diabetic vasculopathy, post capillary resistance or diabetic symptoms associated with insulitis (e.g. hyperglycemia, diuresis, proteinuria and increased nitrite and kallikrein urinary excretion). They may be used to treat inflammatory skin disorders such as psoriasis and eczema. They may be used as smooth muscle relaxants for the treatment of spasm of the gastrointestinal tract or uterus or in the therapy of Crohn's disease, ulcerative colitis or pancreatitis. Such compounds may be used therapeutically to treat hyperreactive airways and to treat inflammatory events associated with airways disease e.g. asthma, and to control, restrict or reverse airways hyperreactivity in asthma. They may be used to treat intrinsic and extrinsic asthma including allergic asthma (atopic or non-atopic) as well as exercise-induced asthma, occupational asthma, asthma post-bacterial infection, other non-allergic asthmas and "wheezy-infant syndrome". They may also be effective against pneumoconiosis, including aluminosis, anthracosis, asbestosis, chalicosis, ptilosis, siderosis, silicosis, tabacosis and byssinosis was well as adult respiratory distress syndrome, chronic obstructive pulmonary or airways disease, bronchitis, allergic rhinitis, and vasomotor rhinitis. Additionally, they may be effective against liver disease, multiple sclerosis, atherosclerosis, Alzheimer's disease, septic shock e.g. as anti-hypovolemic and/or anti-hypotensive agents, cerebral edema, headache, migraine, closed head trauma, irritable bowel syndrome and nephritis. Finally, such compounds are also useful as research tools (*in vivo* and *in vitro*).

SUMMARY OF THE INVENTION

Compounds of this invention represented by Formula I:

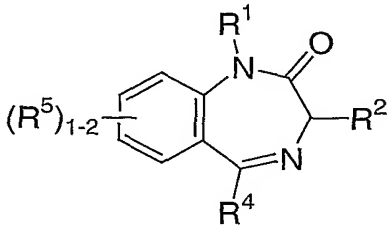


(I)

or a pharmaceutically acceptable salt thereof, are bradykinin B1 antagonist compounds useful in the treatment or prevention of symptoms such as pain and inflammation associated with the bradykinin B1 pathway.

DETAILED DESCRIPTION OF THE INVENTION

The compounds of this invention are represented by Formula I:



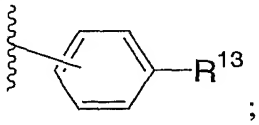
(I)

or a pharmaceutically acceptable salt thereof, wherein:

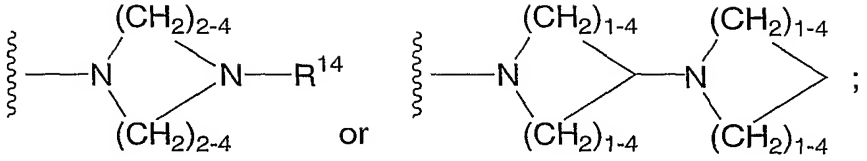
R^1 is H, C_{1-8}alkyl (optionally substituted with 1-9 independent halogens), C_{1-6}alkyloxy–, –C_{1-10}alkylaryl, –C_{0-2}alkyl–C_{3-10}cycloalkyl or C_{2-6}alkenyl;

R^2 is –NHC(O)$NR^{22}R^{23}$, –OC(O)$NR^{22}R^{23}$, –C_{1-3}alkyl-C(O)$NR^{22}R^{23}$ or -NHC(O)R^{23}; or

R^2 is H and R^1 is –C_{1-7}alkyl-C(O)-NH-R^{12};

R^{12} is -C_{2-4}alkyl-R^{13} or  ;

R^{13} is



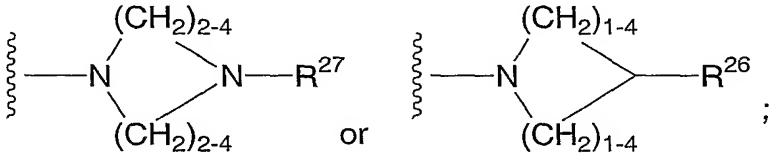
R^{14} is aryl or heteroaryl wherein the aryl or heteroaryl is optionally substituted with 1-2 substituents, each substituent independently is C_{1-6}alkyl, C_{1-6}alkyloxy, C_{1-6}alkylcarboxy-, C_{1-6}alkylamido, OH, halogen, nitro, amino or cyano;

R^{22} is H, C_{1-8}alkyl (optionally substituted with 1-9 independent halogens), C_{1-6}alkyloxy–, –C_{1-10}alkylaryl, –C_{0-2}alkyl–C_{3-10}cycloalkyl, or C_{2-6}alkenyl;

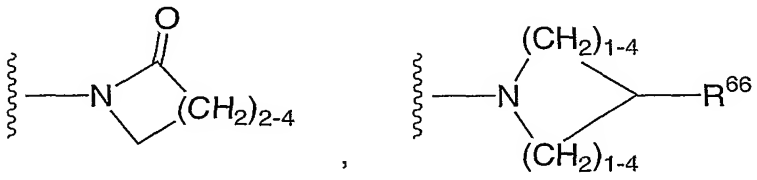
R^{23} is –C_{2-6}alkyl–R^{25}, –C_{1-6}alkyl–R^{31}, –C_{0-4}alkylaryl, or -C_{0-4}alkylheteroaryl, wherein the aryl or heteroaryl is substituted with a group selected from -C≡C-R^{44}, -$(CH_2)_{0-4}$-R^{25} and –C(O)–R^{25};

R^{44} is aryl or heteroaryl, wherein the aryl or heteroaryl is optionally substituted with 1-2 substituents, each substituent independently is C_{1-6}alkyl (optionally substituted with 1-9 independent halogens), C_{1-6}alkyloxy–, C_{1-6}alkyl-carboxy–, C_{1-6}alkylamido–, OH, halogen, nitro, amino or cyano;

R^{25} is



R^{26} is H, –$NR^{66}R^{67}$, –C(O)–O–R^{66}, –C(O)–$NR^{66}R^{67}$, OH,

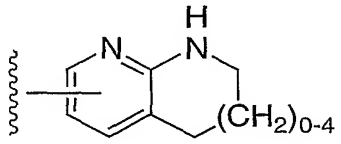


aryl or heteroaryl, wherein the aryl or heteroaryl is optionally substituted with 1-2 substituents, each substituent independently is C_{1-6}alkyl (optionally substituted with 1-9 independent halogens), C_{1-6}alkyloxy–, C_{1-6}alkylcarboxy–, C_{1-6}alkylamido–, OH, halogen, nitro, amino, or cyano;

R^{66} and R^{67} are each independently H, OH, C_{1-8}alkyl (optionally substituted with 1-9 independent halogens), C_{1-6}alkyloxy–, $-C_{1-10}$alkylaryl, $-C_{0-2}$alkyl–C_{3-10}cycloalkyl, or C_{2-6}alkenyl;

R^{27} is $-C_{0-2}$alkyl–C_{3-10}cycloalkyl, $-C_{0-2}$alkylaryl, or $-C_{0-2}$alkylheteroaryl, wherein the aryl or heteroaryl is optionally substituted with 1-2 substituents, each substituent independently is C_{1-6}alkyl (optionally substituted with 1-9 independent halogens), C_{1-6}alkyloxy–, C_{1-6}alkylcarboxy–, C_{1-6}alkylamido–, OH, halogen, nitro, amino or cyano;

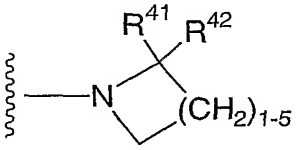
R^{31} is



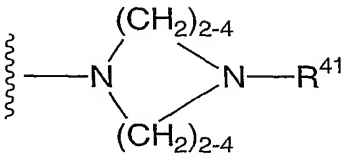
;

R^4 is C_{1-8}alkyl (optionally substituted with 1-9 independent halogens), C_{1-6}alkyloxy–, $-C_{0-3}$alkyl–C_{3-10}cycloalkyl, C_{2-8}alkenyl, $-C_{0-3}$alkylaryl, or $-C_{0-3}$alkylheteroaryl, wherein the aryl or heteroaryl is optionally substituted with 1-3 substituents, each substituent independently is C_{1-6}alkyl (optionally substituted with 1-9 independent halogens), C_{1-6}alkyloxy–, C_{1-6}alkylcarboxy–, C_{1-6}alkylamido–, OH, halogen, nitro, amino, or cyano, or

R^4 is



, or



;

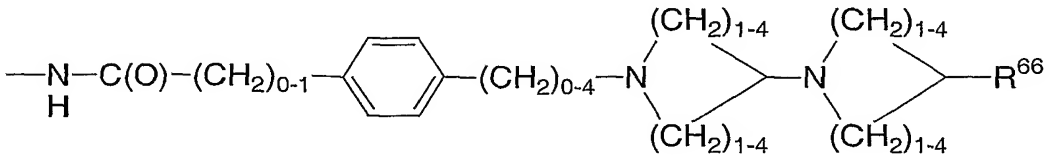
R^{41} and R^{42} are each independently H, C_{1-8}alkyl (optionally substituted with 1-9 independent halogens), C_{1-6}alkyloxy–, $-C_{1-10}$alkylaryl, $-C_{0-2}$alkyl–C_{3-10}cycloalkyl, or C_{2-6}alkenyl;

R^5 is H, nitro, halogen, cyano, OH, amino, C_{1-6}alkylthio–, C_{1-8}alkyl (optionally substituted with 1-9 independent halogens), C_{1-8}alkyloxy–, $-C_{0-10}$alkylaryl, $-C_{0-10}$alkylheteroaryl, $-C(O)-C_{0-2}$alkylaryl, $-C(O)-C_{0-2}$alkylheteroaryl, –C(O)–O–aryl, –C(O)–O–heteroaryl, –C(O)–NH–C_{0-2}alkylaryl, $-C(O)-NH-C_{0-2}$alkylheteroaryl, $-C(O)-N(C_{1-8}alkyl)-C_{0-2}$alkylaryl,

or -C(O)–N(C_{1-8}alkyl)–C_{0-2}alkylheteroaryl, wherein the aryl or heteroaryl is optionally substituted with 1-2 substituents, each substituent independently is C_{1-6}alkyl, C_{1-6}alkyloxy–, C_{1-6}alkylcarboxy–, C_{1-6}alkylamido–, OH, halogen, nitro, amino, or cyano.

In one aspect, the compounds of the present application are represented by Formula I, or a pharmaceutically acceptable salt thereof, wherein:

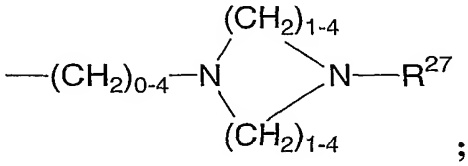
R^2 is



In a second aspect, the compounds of the present application are represented by Formula I, or a pharmaceutically acceptable salt thereof, wherein:

R^2 is –NHC(O)$NR^{22}R^{23}$.

In an embodiment of the second aspect, R^{23} is –C_{0-4}alkylaryl, wherein the aryl is substituted with

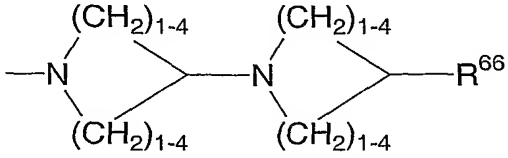


;

R^{27} is –C_{0-2}alkylaryl, or –C_{0-2}alkylheteroaryl, wherein the aryl or heteroaryl is optionally substituted with 1-2 substituents, each substituent independently is C_{1-6}alkyl (optionally substituted with 1-9 independent halogens), C_{1-6}alkyloxy–, C_{1-6}alkylcarboxy–, C_{1-6}alkylamido–, OH, halogen, nitro, amino or cyano;

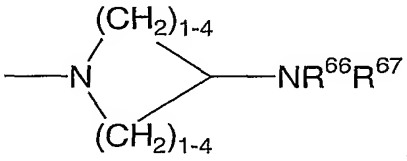
In another embodiment of the second aspect R^{23} is –C_{0-4}alkylaryl, wherein the aryl is substituted with –$(CH_2)_{0-4}$–R^{25} or –C(O)–R^{25};

R^{25} is



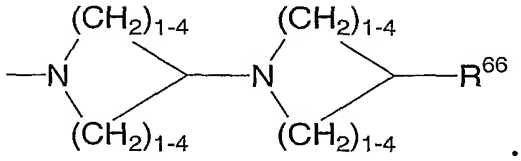
In still another embodiment of the second aspect, R^{23} is -C_{0-4}alkylaryl, wherein the aryl is substituted with $-(CH_2)_{0-4}-R^{25}$ or $-C(O)-R^{25}$;

R^{25} is



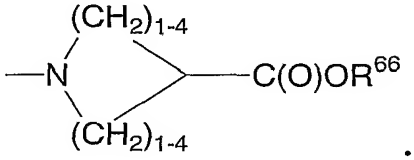
In yet still another embodiment of the second aspect R^{23} is -C_{0-4}alkylheteroaryl, wherein the heteroaryl is substituted with $-(CH_2)_{0-4}-R^{25}$, or $-C(O)-R^{25}$;

R^{25} is



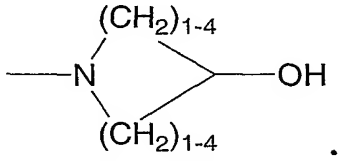
In an embodiment of the second aspect, R^{23} is -C_{0-4}alkylaryl, wherein the aryl is substituted with $-(CH_2)_{0-4}-R^{25}$, or $-C(O)-R^{25}$;

R^{25} is



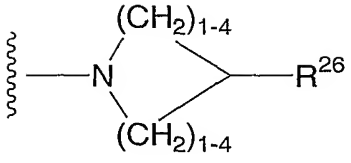
In still another embodiment of the second aspect R^{23} is -C_{0-4}alkylaryl, wherein the aryl is substituted with $-(CH_2)_{0-4}-R^{25}$ or $-C(O)-R^{25}$;

R^{25} is



In still another embodiment of the second aspect, R^{23} is -C_{0-4}alkylaryl, wherein the aryl is substituted with $-(CH_2)_{0-4}-R^{25}$ or $-C(O)-R^{25}$;

R^{25} is

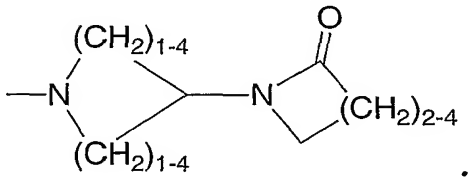


;

R^{26} is aryl, wherein the aryl is optionally substituted with 1-2 substituents, each substituent independently is C_{1-6}alkyl (optionally substituted with 1-9 independent halogens), C_{1-6}alkyloxy–, C_{1-6}alkylcarboxy–, C_{1-6}alkylamido–, OH, halogen, nitro, amino, or cyano;

In yet still another embodiment of the second aspect, R^{23} is -C_{0-4}alkylaryl, wherein the aryl is substituted with –$(CH_2)_{0-4}$–R^{25} or –C(O)–R^{25};

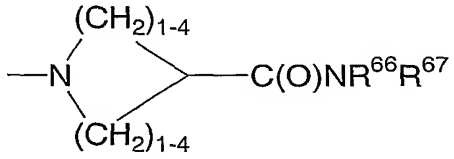
R^{25} is



.

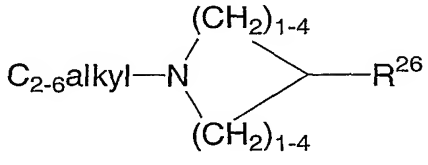
In still another further embodiment of the second aspect, R^{23} is -C_{0-4}alkylaryl, wherein the aryl is substituted with –$(CH_2)_{0-4}$–R^{25} or –C(O)–R^{25};

R^{25} is



.

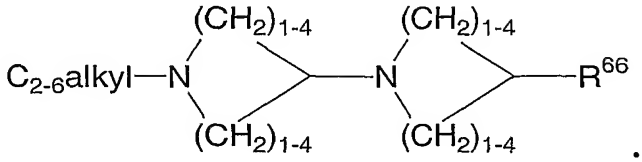
In another further embodiment of the second aspect, R^{23} is



;

R^{26} is aryl or heteroaryl, wherein the aryl or heteroaryl is optionally substituted with 1-2 substituents, each substituent independently is C_{1-6}alkyl (optionally substituted with 1-9 independent halogens), C_{1-6}alkyloxy–, C_{1-6}alkylcarboxy–, C_{1-6}alkylamido–, OH, halogen, nitro, amino, or cyano.

In yet another further embodiment of the second aspect, R^{23} is



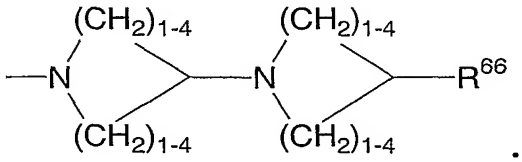
In still yet another embodiment of the second aspect, R^{23} is -C_{0-4}alkylaryl, wherein the aryl is substituted with

In a third aspect, the compounds of the present application are represented by Formula I, or a pharmaceutically acceptable salt thereof, wherein:

R^2 is –O–C(O)$NR^{22}R^{23}$ or –C_{1-3}alkyl–C(O)$NR^{22}R^{23}$.

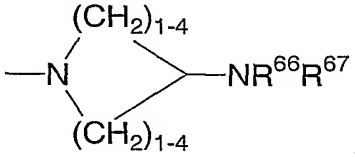
In one embodiment of the third aspect, R^2 is –O–C(O)$NR^{22}R^{23}$; R^{23} is –C_{0-4}alkylaryl, wherein the aryl is optionally substituted with 1-2 substituents, each substituent independently is –$(CH_2)_{0-4}$–R^{25}, or –C(O)–R^{25};

R^{25} is



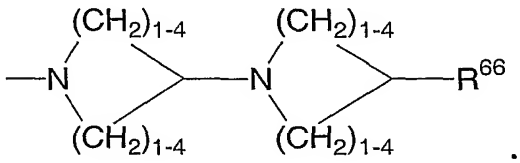
In another embodiment of the third aspect, R^2 is -C_{1-3}alkyl-C(O)$NR^{22}R^{23}$; R^{23} is –C_{0-4}alkylaryl, wherein the aryl is substituted with –$(CH_2)_{0-4}$–R^{25} or –C(O)–R^{25};

R^{25} is



In still another embodiment of the third aspect, R^2 is $-C_{1-3}alkyl-C(O)NR^{22}R^{23}$; R^{23} is $-C_{0-4}alkylaryl$, wherein the aryl is substituted with $-(CH_2)_{0-4}-R^{25}$ or $-C(O)-R^{25}$;

R^{25} is

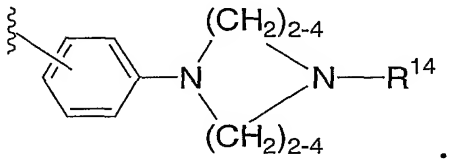


.

In a fourth aspect, the compounds of the present application are represented by Formula I, or a pharmaceutically acceptable salt thereof, wherein:

R^2 is H and R^1 is $-C_{1-7}alkyl-C(O)-NH-R^{12}$.

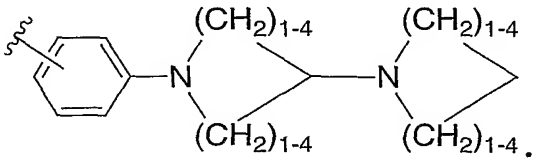
In an embodiment of the fourth aspect, R^{12} is



.

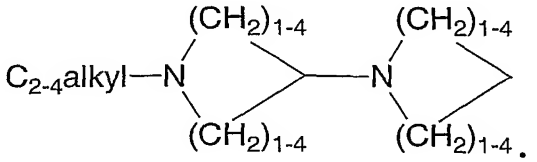
R^{14} is heteroaryl, wherein the heteroaryl is optionally substituted with 1-2 substituents, each substituent independently is $C_{1-6}alkyl$, $C_{1-6}alkyloxy-$, $C_{1-6}alkylcarboxy-$, $C_{1-6}alkylamido-$, OH, halogen, nitro, amino, or cyano;

In another embodiment of the fourth aspect, R^{12} is



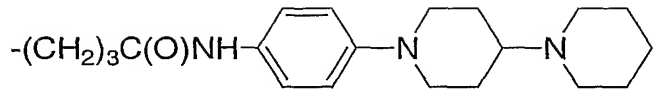
.

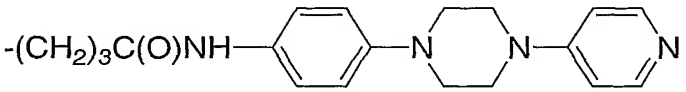
In still another embodiment of the fourth aspect, R^{12} is



.

It is advantageous that for compounds of Formula I R^2 is H and R^1 is


, or


; or

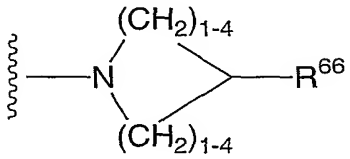
R^2 is –NH–C(O)–NHR^{23} and R^1 is propyl, cyclopropylmethyl or 2,2,2-trifluoroethyl,

R^{23} is aryl or heteroaryl, wherein the aryl or heteroaryl is substituted with


;

R^{26} is $NR^{66}R^{67}$, aryl or heteroaryl, wherein the aryl or heteroaryl is optionally substituted with 1-2 substituents, each substituent independently is C_{1-6}alkyl (optionally substituted with 1-9 independent halogens), C_{1-6}alkyloxy, C_{1-6}alkylcarboxy, C_{1-6}alkylamido, OH, halogen, nitro, amino, or cyano, or,

R^{26} is


;

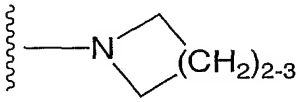
R^{66} and R^{67} are each independently H, C_{1-8}alkyl (optionally substituted with 1-9 independent halogens), C_{1-6}alkyloxy, C_{1-10}alkylaryl, -C_{0-2}alkyl-C_{3-6}cycloalkyl, C_{2-6}alkenyl;

R^{27} is -C_{0-2}alkyl-C_{3-6}cycloalkyl, C_{0-2}alkylaryl, C_{0-2}alkylheteroaryl, wherein the aryl or heteroaryl is optionally substituted with 1-2 substituents, each substituent independently is C_{1-6}alkyl (optionally substituted with 1-9 independent halogens), C_{1-6}alkyloxy, C_{1-6}alkylcarboxy, C_{1-6}alkylamido, OH, halogen, nitro, amino or cyano;

R^4 is C_{0-3}alkyl-C_{3-10}cycloalkyl, C_{0-3}alkylaryl, C_{0-3}alkylheteroaryl, wherein the aryl or heteroaryl is optionally substituted with 1-3 substituents, each substituent independently is C_{1-6}alkyl (optionally substituted with 1-9 independent

halogens), C_{1-6}alkoxy, C_{1-6}alkylcarboxy, C_{1-6}alkylamido, OH, halogen, nitro, amino, or cyano, or

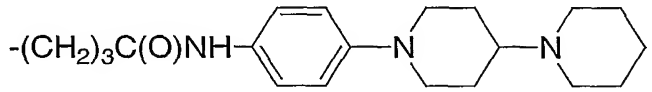
R^4 is



; and

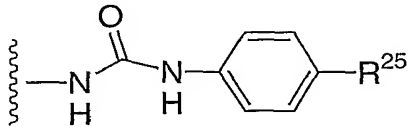
R^5 is H or a single substituent, at the 7-position of the benzodiazepine core, chosen from among the following list: nitro, halogen, cyano, OH, amino, C_{1-6}alkylthio, C_{1-8}alkyl (optionally substituted with 1-9 independent halogens), C_{1-8}alkoxy, $-C_{0-10}$alkylaryl, $-C_{0-10}$alkylheteroaryl, $-C(O)-C_{0-2}$alkylaryl, $-C(O)-C_{0-2}$alkylheteroaryl, $-C(O)-O-$aryl, $-C(O)-O-$heteroaryl, $-C(O)-NH-C_{0-2}$alkylaryl, $-C(O)-NH-C_{0-2}$alkylheteroaryl, $-C(O)-N(C_{1-8}alkyl)-C_{0-2}$alkylaryl, $-C(O)-N(C_{1-8}alkyl)-C_{0-2}$alkylheteroaryl, wherein the aryl or heteroaryl is optionally substituted with 1-2 substituents, each substituent independently is C_{1-6}alkyl, C_{1-6}alkoxy, C_{1-6}alkylcarboxy, C_{1-6}alkylamido, OH, halogen, nitro, amino, or cyano.

More advantageously, R^2 is H and R^1 is



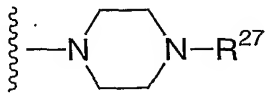
; or

R^1 is propyl and R^2 is



;

R^{25} is



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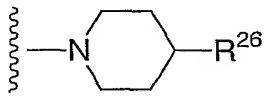
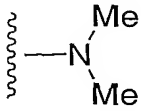


;

R^{26} is



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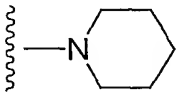


;

R^{27} is 4-pyridyl;

R^4 is cyclohexyl, $-CH_2-CH_2-$phenyl, or 4-methylphenyl; and

R^5 is H.

Another aspect of the present application provides a compound selected from the group and pharmaceutically acceptable salts thereof:

N-(1-methyl-5-phenyl-2-oxo-2,3-dihydro-1H-1,4-benzodiazepin-3-yl)-4-(n-pentyl)benzamide (Example 1.1);

N-(1-methyl-5-(2-fluorophenyl)-2-oxo-2,3-dihydro-1H-1,4-benzodiazepin-3-yl)-4-(n-pentyl)benzamide (Example 1.2);

N-(1-isopropyl-5-phenyl-2-oxo-2,3-dihydro-1H-1,4-benzodiazepin-3-yl)-3-bromobenzamide (Example 1.3);

N-(1-isopropyl-5-phenyl-2-oxo-2,3-dihydro-1H-1,4-benzodiazepin-3-yl)-3-(trifluoromethyl)benzeneacetamide (Example 1.4);

N-(5-cyclohexyl-2-oxo-2,3-dihydro-1H-1,4-benzodiazepin-3-yl)-2-(phenoxy)benzeneacetamide (Example 1.5);

N-(5-(2-flurophenyl)-2-oxo-2,3-dihydro-1H-1,4-benzodiazepin-3-yl)-3-methyl-2-indencarboxamide (Example 1.6);

N-(5-(2-fluorophenyl)-2-oxo-2,3-dihydro-1H-1,4-benzodiazepin-3-yl)-benzamide (Example 1.7);

N-(1-methyl-5-phenyl-2-oxo-2,3-dihydro-1H-1,4-benzodiazepin-3-yl)-cyclohexanecarboxamide (Example 1.8);

N-(1-propyl-5-cyclohexyl-2-oxo-2,3-dihydro-1H-1,4-benzodiazepin-3-yl)-4-(dimethylamino)benzamide (Example 1.9);

N-(1-propyl-5-cyclohexyl-2-oxo-2,3-dihydro-1H-1,4-benzodiazepin-3-yl)-1H-5-indolecarboxamide (Example 1.10);

N-[2-oxo-5-phenyl-1-isopropyl-2,3-dihydro-1H-1,4-benzodiazepin-3-yl]-N'-[4-((3-(dimethylamino)propyl(methyl)amino)phenyl]urea, (Example 5.1);

N-[2-oxo-5-isopropyl-1-propyl-2,3-dihydro-1H-1,4-benzodiazepin-3-yl]-N'-[4-((3-(dimethylamino)propyl(methyl)amino)phenyl]urea, (Example 5.2);

N-[2-oxo-5-cyclohexyl-1-propyl-2,3-dihydro-1H-1,4-benzodiazepin-3-yl]-N'-[4-((3-(dimethylamino)propyl(methyl)amino)phenyl]urea, (Example 5.3);

N-[2-oxo-5-cyclohexyl-1-propyl-2,3-dihydro-1H-1,4-benzodiazepin-3-yl]-N'-[4-(2-(piperidin-1-yl)ethoxy)phenyl]urea, (Example 7.6);

N-[2-oxo-5-phenyl-1-ethyl-2,3-dihydro-1H-1,4-benzodiazepin-3-yl]-N'-(3-methoxyphenyl)urea, (Example 8.1);

N-[2-oxo-5-isopropyl-1-propyl-2,3-dihydro-1H-1,4-benzodiazepin-3-yl]-N'-[4-(morpholin-4-yl)phenyl]urea, (Example 8.2);

N-[2-oxo-5-cyclohexyl-1-propyl-2,3-dihydro-1H-1,4-benzodiazepin-3-yl]-N'-[4-(morpholin-4-yl)phenyl]urea, (Example 8.3);

N-[2-oxo-5-cyclohexyl-1-propyl-2,3-dihydro-1H-1,4-benzodiazepin-3-yl]-N'-[4-(piperidin-1-yl)phenyl]urea, (Example 8.4);

N-[2-oxo-5-cyclohexyl-1-propyl-2,3-dihydro-1H-1,4-benzodiazepin-3-yl]-N'-(3-pyridyl)urea, (Example 8.5);

Benzyl 5-tert-butyl-1-isobutyl-2-oxo-2,3-dihydro-1H-1,4-benzodiazepin-3-ylcarbamate (Example 29);

N-[5-(4-methylpiperazin-1-yl)-2-oxo-1-propyl-2,3-dihydro-1H-1,4-benzodiazepin-3-yl]-N'-(5-methyl-1,3,4-thiadiazol-2-yl)urea (Example 30); and

N-(5-azepan-1-yl-1-methyl-2-oxo-2,3-dihydro-1H-1,4-benzodiazepin-3-yl)-4-phenylbutanamide (Example 32).

Preferred compounds are:

N-[4-(1,4'-bipiperidin-1'-yl)phenyl]-4-(5-cyclohexyl-2-oxo-2,3-dihydro-1H-1,4-benzodiazepin-1-yl)butanamide,

N-[2-oxo-5-(2-phenylethyl)-1-propyl-2,3-dihydro-1H-1,4-benzodiazepin-3-yl]-N'-[4-(4-pyridin-4-ylpiperazin-1-yl)phenyl]urea,

N-[4-(1,4'-bipiperidin-1'-yl)phenyl]-N'-(5-cyclohexyl-2-oxo-1-propyl-2,3-dihydro-1H-1,4-benzodiazepin-3-yl)urea,

N-[4-(1,4'-bipiperidin-1'-yl)phenyl]-N'-[5-(4-methylphenyl)-2-oxo-1-propyl-2,3-dihydro-1H-1,4-benzodiazepin-3-yl]urea,

or pharmaceutically acceptable salts thereof.

As used herein, "alkyl" as well as other groups having the prefix "alk" such as, for example, alkoxy, alkanoyl, alkenyl, alkynyl and the like, means carbon chains which may be linear or branched or combinations thereof. Examples of alkyl groups include methyl, ethyl, propyl, isopropyl, butyl, sec- and tert-butyl, pentyl, hexyl, heptyl and the like. "Alkenyl", "alkynyl" and other like terms include carbon chains containing at least one unsaturated C-C bond.

The term "cycloalkyl" means carbocycles containing no heteroatoms, and includes mono-, bi- and tricyclic saturated carbocycles, as well as fused ring systems. Such fused ring systems can include one ring that is partially or fully

unsaturated such as a benzene ring to form fused ring systems such as benzofused carbocycles. Cycloalkyl includes such fused ring systems as spirofused ring systems. Examples of cycloalkyl include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, decahydronaphthalene, adamantane, indanyl, indenyl, fluorenyl, 1,2,3,4-tetrahydronaphthalene and the like. Similarly, "cycloalkenyl" means carbocycles containing no heteroatoms and at least one non-aromatic C-C double bond, and include mono-, bi- and tricyclic partially saturated carbocycles, as well as benzofused cycloalkenes. Examples of cycloalkenyl include cyclohexenyl, indenyl, and the like.

The term "C_0" means that the carbon is not present. Thus, "C_0-C_5" means that there are from none to five carbons present – that is, five, four, three, two, one, or no carbons present. When no carbons are present in a linking alkyl group, the link is a direct bond. When no carbons are present in a terminal alkyl group, the terminus is hydrogen.

The term "aryl" is an aromatic mono- or bicyclic carbocycle having from 6 to 10 carbon atoms, optionally fused to a 4- to 6-membered non-aromatic ring containing 0-3 heteroatoms selected from N, O and S(O)m. Examples include phenyl and naphthyl.

"Heteroaryl" is a mono-or bicyclic aromatic ring containing from 1 to 6 heteroatoms independently selected from N, O and S wherein each ring has five or six ring atoms. Examples of heteroaryl include pyridyl, pyrimidinyl, pyrrolyl, furyl, thienyl, imidazolyl, thiazolyl, thiadiazolyl, triazolyl, tetrazolyl, oxadiazolyl, oxazolyl, imidazolidinyl, pyrazolyl, isoxazolyl, benzothiadiazolyl, indolyl, indolinyl, benzodioxolyl, benzodioxanyl, benzothiophenyl, benzofuranyl, benzimidazolyl, benzisoxazolyl, benzothiazolyl, quinolinyl, benzotriazolyl, benzoxazolyl, purinyl, furopyridine and thienopyridine.

The term "composition", as in pharmaceutical composition, is intended to encompass a product comprising the active ingredient(s), and the inert ingredient(s) that make up the carrier, as well as any product which results, directly or indirectly, from combination, complexation or aggregation of any two or more of the ingredients, or from dissociation of one or more of the ingredients, or from other types of reactions or interactions of one or more of the ingredients. Accordingly, the pharmaceutical compositions of the present invention encompass any composition made by admixing a compound of the present invention and a pharmaceutically acceptable carrier.

The term "optionally substituted" is intended to include both substituted and unsubstituted. Thus, for example, optionally substituted aryl could represent a pentafluorophenyl or a phenyl ring.

Compounds described herein may contain one or more asymmetric centers and may thus give rise to diastereomers and optical isomers. The present invention includes all such possible diastereomers as well as their racemic mixtures, their substantially pure resolved enantiomers, all possible geometric isomers, and pharmaceutically acceptable salts thereof. The above Formula I is shown without a definitive stereochemistry at certain positions. The present invention includes all stereoisomers of Formula I, and pharmaceutically acceptable salts thereof. Further, mixtures of stereoisomers as well as isolated specific stereoisomers are also included. During the course of the synthetic procedures used to prepare such compounds, or in using racemization or epimerization procedures known to those skilled in the art, the products of such procedures can be a mixture of stereoisomers.

The term "pharmaceutically acceptable salts" refers to salts prepared from pharmaceutically acceptable non-toxic bases or acids. When the compound of the present invention is acidic, its corresponding salt can be conveniently prepared from pharmaceutically acceptable non-toxic bases, including inorganic bases and organic bases. Salts derived from such inorganic bases include aluminum, ammonium, calcium, copper (ic and ous), ferric, ferrous, lithium, magnesium, manganese (ic and ous), potassium, sodium, zinc and the like salts. Particularly preferred are the ammonium, calcium, magnesium, potassium and sodium salts. Salts derived from pharmaceutically acceptable organic non-toxic bases include salts of primary, secondary, and tertiary amines, as well as cyclic amines and substituted amines such as naturally occurring and synthesized substituted amines. Other pharmaceutically acceptable organic non-toxic bases from which salts can be formed include ion exchange resins such as, for example, arginine, betaine, caffeine, choline, N,N'-dibenzylethylenediamine, diethylamine, 2-diethylaminoethanol, 2-dimethylaminoethanol, ethanolamine, ethylenediamine, N-ethylmorpholine, N-ethylpiperidine, glucamine, glucosamine, histidine, hydrabamine, isopropylamine, lysine, methylglucamine, morpholine, piperazine, piperidine, polyamine resins, procaine, purines, theobromine, triethylamine, trimethylamine, tripropylamine, tromethamine and the like.

When the compound of the present invention is basic, its corresponding salt can be conveniently prepared from pharmaceutically acceptable

non-toxic acids, including inorganic and organic acids. Such acids include, for example, acetic, benzenesulfonic, benzoic, camphorsulfonic, citric, ethanesulfonic, fumaric, gluconic, glutamic, hydrobromic, hydrochloric, isethionic, lactic, maleic, malic, mandelic, methanesulfonic, mucic, nitric, pamoic, pantothenic, phosphoric, succinic, sulfuric, tartaric, p-toluenesulfonic acid and the like. Particularly preferred are citric, hydrobromic, hydrochloric, maleic, phosphoric, sulfuric, and tartaric acids.

The pharmaceutical compositions of the present invention comprise a compound of the present invention (or pharmaceutically acceptable salts thereof) as an active ingredient, a pharmaceutically acceptable carrier and optionally other therapeutic ingredients or adjuvants. The compositions include compositions suitable for oral, rectal, topical, and parenteral (including subcutaneous, intramuscular, and intravenous) administration, although the most suitable route in any given case will depend on the particular host, and nature and severity of the conditions for which the active ingredient is being administered. The pharmaceutical compositions may be conveniently presented in unit dosage form and prepared by any of the methods well known in the art of pharmacy.

In practice, the compounds of this invention or pharmaceutically acceptable salts thereof can be combined as the active ingredient in intimate admixture with a pharmaceutical carrier according to conventional pharmaceutical compounding techniques. The carrier may take a wide variety of forms depending on the form of preparation desired for administration, e.g., oral or parenteral (including intravenous). Thus, the pharmaceutical compositions of the present invention can be presented as discrete units suitable for oral administration such as capsules, cachets or tablets each containing a predetermined amount of the active ingredient. Further, the compositions can be presented as a powder, as granules, as a solution, as a suspension in an aqueous liquid, as a non-aqueous liquid, as an oil-in-water emulsion or as a water-in-oil liquid emulsion. In addition to the common dosage forms set out above, the compounds of the present invention or pharmaceutically acceptable salts thereof, may also be administered by controlled release means and/or delivery devices. The compositions may be prepared by any of the methods of pharmacy. In general, such methods include a step of bringing into association the active ingredient with the carrier that constitutes one or more necessary ingredients. In general, the compositions are prepared by uniformly and intimately admixing the active ingredient with liquid carriers or finely divided solid carriers or both. The product can then be conveniently shaped into the desired presentation.

Thus, the pharmaceutical compositions of this invention may include a pharmaceutically acceptable carrier and a compound of the present invention or a pharmaceutically acceptable salt thereof. The compounds of the present invention or pharmaceutically acceptable salts thereof, can also be included in pharmaceutical compositions in combination with one or more other therapeutically active compounds.

The pharmaceutical carrier employed can be, for example, a solid, liquid, or gas. Examples of solid carriers include lactose, terra alba, sucrose, talc, gelatin, agar, pectin, acacia, magnesium stearate, and stearic acid. Examples of liquid carriers are sugar syrup, peanut oil, olive oil, and water. Examples of gaseous carriers include carbon dioxide and nitrogen.

In preparing the compositions for oral dosage form, any convenient pharmaceutical media may be employed. For example, water, glycols, oils, alcohols, flavoring agents, preservatives, coloring agents and the like may be used to form oral liquid preparations such as suspensions, elixirs and solutions; while carriers such as starches, sugars, microcrystalline cellulose, diluents, granulating agents, lubricants, binders, disintegrating agents, and the like may be used to form oral solid preparations such as powders, capsules and tablets. Because of their ease of administration, tablets and capsules are the preferred oral dosage units whereby solid pharmaceutical carriers are employed. Optionally, tablets may be coated by standard aqueous or nonaqueous techniques

A tablet containing the composition of this invention may be prepared by compression or molding, optionally with one or more accessory ingredients or adjuvants. Compressed tablets may be prepared by compressing, in a suitable machine, the active ingredient in a free-flowing form such as powder or granules, optionally mixed with a binder, lubricant, inert diluent, surface active or dispersing agent. Molded tablets may be made by molding in a suitable machine, a mixture of the powdered compound moistened with an inert liquid diluent. Each tablet preferably contains from about 0.1mg to about 500mg of the active ingredient and each cachet or capsule preferably containing from about 0.1 to about 500mg of the active ingredient. The tablet, cachet, or capsule can each contain, for example, 0.1mg, 0.5mg, 1mg, 3mg, 5mg, 10mg, 25mg, 50mg, 100mg, 125mg, 250mg, or 500mg of active ingredient.

Pharmaceutical compositions of the present invention suitable for parenteral administration may be prepared as solutions or suspensions of the active

compounds in water. A suitable surfactant can be included such as, for example, hydroxypropylcellulose. Dispersions can also be prepared in glycerol, liquid polyethylene glycols, and mixtures thereof in oils. Further, a preservative can be included to prevent the detrimental growth of microorganisms.

Pharmaceutical compositions of the present invention suitable for injectable use include sterile aqueous solutions or dispersions. Furthermore, the compositions can be in the form of sterile powders for the extemporaneous preparation of such sterile injectable solutions or dispersions. In all cases, the final injectable form must be sterile and must be effectively fluid for easy syringability. The pharmaceutical compositions must be stable under the conditions of manufacture and storage; thus, preferably should be preserved against the contaminating action of microorganisms such as bacteria and fungi. The carrier can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (e.g. glycerol, propylene glycol and liquid polyethylene glycol), vegetable oils, and suitable mixtures thereof.

Pharmaceutical compositions of the present invention can be in a form suitable for topical use such as, for example, an aerosol, cream, ointment, lotion, dusting powder, or the like. Further, the compositions can be in a form suitable for use in transdermal devices. These formulations may be prepared, utilizing a compound of this invention, or pharmaceutically acceptable salts thereof, via conventional processing methods. As an example, a cream or ointment is prepared by mixing hydrophilic material and water, together with about 5 wt% to about 10 wt% of the compound, to produce a cream or ointment having a desired consistency.

Pharmaceutical compositions of this invention can be in a form suitable for rectal administration wherein the carrier is a solid. It is preferable that the mixture forms unit dose suppositories. Suitable carriers include cocoa butter and other materials commonly used in the art. The suppositories may be conveniently formed by first admixing the composition with the softened or melted carrier(s) followed by chilling and shaping in moulds.

In addition to the aforementioned carrier ingredients, the pharmaceutical formulations described above may include, as appropriate, one or more additional carrier ingredients such as diluents, buffers, flavoring agents, binders, surface-active agents, thickeners, lubricants, preservatives (including anti-oxidants) and the like. Furthermore, other adjuvants can be included to render the formulation isotonic with the blood of the intended recipient. Compositions containing a

compound described by Formula I, or pharmaceutically acceptable salts thereof, may also be prepared in powder or liquid concentrate form.

Experimental Protocols

Assessing the Activity of Selected Compounds to Bind to the Bradykinin B1 and B2 Receptors

Radioligand binding assays are performed using membranes from CHO cells that stably express the human, rabbit, rat, or dog B1 receptors or CHO cells that express the human B2 receptor. For all receptor types, cells are harvested from culture flasks in PBS/1mM EDTA and centrifuged at 1000xg for 10 minutes. The cell pellets are homogenized with a polytron in ice cold 20mM HEPES, 1mM EDTA, pH 7.4 (lysis buffer) and centrifuged at 20,000xg for 20 minutes. The membrane pellets are rehomogenized in lysis buffer, centrifuged again at 20,000xg and the final pellets are resuspended at 5mg protein/ml in assay buffer (120mM NaCl, 5mM KCl, 20mM HEPES, pH 7.4) supplemented with 1% BSA and frozen at –80°C.

On the day of assay, membranes are centrifuged at 14,000xg for 5 minutes and resuspended to the desired protein concentration in assay buffer containing 100nM enaliprilat, 140μg/mL bacitracin and 0.1% BSA. 3H-des-arg10, leu9 kallidin is the radioligand used for the human and rabbit B1 receptors, 3H-des-arg10 kallidin is used for the rat and dog B1 receptors, and 3H-bradykinin is used to label the human B2 receptor.

For all assays, compounds are diluted from DMSO stock solutions with 4μL added to assay tubes for a final DMSO concentration of 2%. This is followed by the addition of 100μL radioligand and 100μL of the membrane suspension. Nonspecific binding for the B1 receptor binding assays is determined using 1μM des-arg10 kallidin and nonspecific binding for the B2 receptor is determined with 1μM bradykinin. Tubes are incubated at room temperature (22°C) for 60 minutes followed by filtration using a Tomtec 96-well harvesting system. Radioactivity retained by the filter is counted using a Wallac Beta-plate scintillation counter.

The compounds of this invention have potency in the above assay as demonstrated by results of less than 5μM. It is advantageous that the assay results be less than 1μM, even more advantageous for the results be less than 0.5μM.

Accordingly, the compounds of this invention are useful in the treatment of pain and inflammation. The compounds would be effective in the treatment or prevention of pain including, for example, bone and joint pain (osteoarthritis), repetitive motion pain, dental pain, cancer pain, myofascial pain (muscular injury, fibromyalgia), perioperative pain (general surgery, gynecological) and chronic pain. In particular, inflammatory pain such as, for example, inflammatory airways disease (chronic obstructive pulmonary disease) would be effectively treated by the bradykinin B1 antagonist compounds of this invention.

Further, the compounds of this invention – by being bradykinin B1 antagonists – can additionally be used to treat asthma, inflammatory bowel disease, rhinitis, pancreatitis, cystitis (interstitial cystitis), uveitis, inflammatory skin disorders, rheumatoid arthritis and edema resulting from trauma associated with burns, sprains or fracture. They may be used subsequent to surgical intervention (e.g. as post-operative analgesics) and to treat inflammatory pain of varied origins (e.g. osteoarthritis, rheumatoid arthritis, rheumatic disease, teno-synovitis and gout) as well as for the treatment of pain associated with angina, menstruation or cancer. They may be used to treat diabetic vasculopathy, post capillary resistance or diabetic symptoms associated with insulitis (e.g. hyperglycemia, diuresis, proteinuria and increased nitrite and kallikrein urinary excretion). They may be used to treat inflammatory skin disorders such as psoriasis and eczema. They may be used as smooth muscle relaxants for the treatment of spasm of the gastrointestinal tract or uterus or in the therapy of Crohn's disease, ulcerative colitis or pancreatitis. Such compounds may be used therapeutically to treat hyperreactive airways and to treat inflammatory events associated with airways disease e.g. asthma, and to control, restrict or reverse airways hyperreactivity in asthma. They may be used to treat intrinsic and extrinsic asthma including allergic asthma (atopic or non-atopic) as well as exercise-induced asthma, occupational asthma, asthma post-bacterial infection, other non-allergic asthmas and "wheezy-infant syndrome". They may also be effective against pneumoconiosis, including aluminosis, anthracosis, asbestosis, chalicosis, ptilosis, siderosis, silicosis, tabacosis and byssinosis was well as adult respiratory distress syndrome, chronic obstructive pulmonary or airways disease, bronchitis, allergic rhinitis, and vasomotor rhinitis. Additionally, they may be effective against liver disease, multiple sclerosis, atherosclerosis, Alzheimer's disease, septic shock e.g. as anti-hypovolemic and/or anti-hypotensive agents, cerebral edema, headache including cluster headache, migraine including prophylactic and acute use, closed head trauma, irritable bowel

syndrome and nephritis. Finally, such compounds are also useful as research tools (*in vivo* and *in vitro*).

The compounds of this invention are useful in the treatment of pain and inflammation by the administration of a tablet, cachet, or capsule each containing, for example, 0.1mg, 0.5mg, 1mg, 3mg, 5mg, 10mg, 25mg, 50mg, 100mg, 125mg, 250mg, or 500mg of a compound of this invention once every three to four hours, once, twice or three times a day, or (in an extended release formulation) once, twice or three times a week.

The compounds would be effective in the treatment or prevention of pain including, for example, bone and joint pain (osteoarthritis), repetitive motion pain, dental pain, cancer pain, myofascial pain (muscular injury, fibromyalgia), perioperative pain (general surgery, gynecological) and chronic pain by the administration of a tablet, cachet, or capsule each containing, for example, 0.1mg, 0.5mg, 1mg, 3mg, 5mg, 10mg, 25mg, 50mg, 100mg, 125mg, 250mg, or 500mg of a compound of this invention once every three to four hours, once, twice or three times a day, or (in an extended release formulation) once, twice or three times a week.

In particular, inflammatory pain such as, for example, inflammatory airways disease (chronic obstructive pulmonary disease) would be effectively treated by the bradykinin B1 antagonist compounds of this invention by the administration of a tablet, cachet, or capsule each containing, for example, 0.1mg, 0.5mg, 1mg, 3mg, 5mg, 10mg, 25mg, 50mg, 100mg, 125mg, 250mg, or 500mg of a compound of this invention once every three to four hours, once, twice or three times a day, or (in an extended release formulation) once, twice or three times a week.

Further, the compounds of this invention – by being bradykinin B1 antagonists – can additionally be used to treat asthma, inflammatory bowel disease, rhinitis, pancreatitis, cystitis (interstitial cystitis), uveitis, inflammatory skin disorders, rheumatoid arthritis and edema resulting from trauma associated with burns, sprains or fracture by the administration of a tablet, cachet, or capsule each containing, for example, 0.1mg, 0.5mg, 1mg, 3mg, 5mg, 10mg, 25mg, 50mg, 100mg, 125mg, 250mg, or 500mg of a compound of this invention once every three to four hours, once, twice or three times a day, or (in an extended release formulation) once, twice or three times a week.

They may be used subsequent to surgical intervention (e.g. as post-operative analgesics) and to treat inflammatory pain of varied origins (e.g. osteoarthritis, rheumatoid arthritis, rheumatic disease, teno-synovitis and gout) as well

as for the treatment of pain associated with angina, menstruation or cancer by the administration of a tablet, cachet, or capsule each containing, for example, 0.1mg, 0.5mg, 1mg, 3mg, 5mg, 10mg, 25mg, 50mg, 100mg, 125mg, 250mg, or 500mg of a compound of this invention once every three to four hours, once, twice or three times a day, or (in an extended release formulation) once, twice or three times a week.

They may be used to treat diabetic vasculopathy, post capillary resistance or diabetic symptoms associated with insulitis (e.g. hyperglycemia, diuresis, proteinuria and increased nitrite and kallikrein urinary excretion) by the administration of a tablet, cachet, or capsule each containing, for example, 0.1mg, 0.5mg, 1mg, 3mg, 5mg, 10mg, 25mg, 50mg, 100mg, 125mg, 250mg, or 500mg of a compound of this invention once every three to four hours, once, twice or three times a day, or (in an extended release formulation) once, twice or three times a week.

They may be used to treat inflammatory skin disorders such as psoriasis and eczema by the administration of a tablet, cachet, or capsule each containing, for example, 0.1mg, 0.5mg, 1mg, 3mg, 5mg, 10mg, 25mg, 50mg, 100mg, 125mg, 250mg, or 500mg of a compound of this invention once every three to four hours, once, twice or three times a day, or (in an extended release formulation) once, twice or three times a week.

They may be used as smooth muscle relaxants for the treatment of spasm of the gastrointestinal tract or uterus or in the therapy of Crohn's disease, ulcerative colitis or pancreatitis by the administration of a tablet, cachet, or capsule each containing, for example, 0.1mg, 0.5mg, 1mg, 3mg, 5mg, 10mg, 25mg, 50mg, 100mg, 125mg, 250mg, or 500mg of a compound of this invention once every three to four hours, once, twice or three times a day, or (in an extended release formulation) once, twice or three times a week.

Such compounds may be used therapeutically to treat hyperreactive airways and to treat inflammatory events associated with airways disease e.g. asthma, and to control, restrict or reverse airways hyperreactivity in asthma by the administration of a tablet, cachet, or capsule each containing, for example, 0.1mg, 0.5mg, 1mg, 3mg, 5mg, 10mg, 25mg, 50mg, 100mg, 125mg, 250mg, or 500mg of a compound of this invention once every three to four hours, once, twice or three times a day, or (in an extended release formulation) once, twice or three times a week.

They may be used to treat intrinsic and extrinsic asthma including allergic asthma (atopic or non-atopic) as well as exercise-induced asthma, occupational asthma, asthma post-bacterial infection, other non-allergic asthmas and

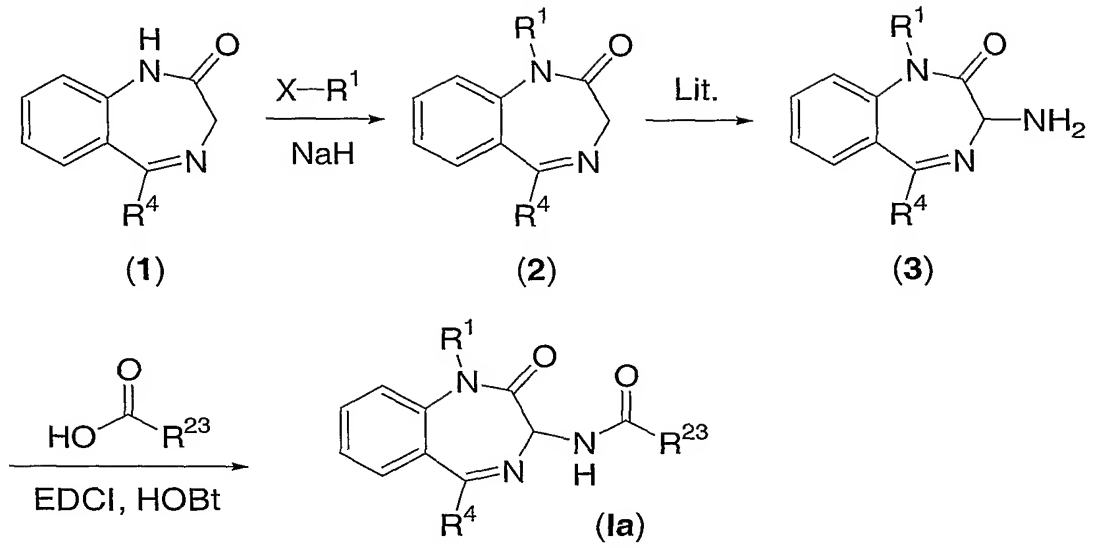
"wheezy-infant syndrome" by the administration of a tablet, cachet, or capsule each containing, for example, 0.1mg, 0.5mg, 1mg, 3mg, 5mg, 10mg, 25mg, 50mg, 100mg, 125mg, 250mg, or 500mg of a compound of this invention once every three to four hours, once, twice or three times a day, or (in an extended release formulation) once, twice or three times a week.

They may also be effective against pneumoconiosis, including aluminosis, anthracosis, asbestosis, chalicosis, ptilosis, siderosis, silicosis, tabacosis and byssinosis was well as adult respiratory distress syndrome, chronic obstructive pulmonary or airways disease, bronchitis, allergic rhinitis, and vasomotor rhinitis by the administration of a tablet, cachet, or capsule each containing, for example, 0.1mg, 0.5mg, 1mg, 3mg, 5mg, 10mg, 25mg, 50mg, 100mg, 125mg, 250mg, or 500mg of a compound of this invention once every three to four hours, once, twice or three times a day, or (in an extended release formulation) once, twice or three times a week.

Additionally, they may be effective against liver disease, multiple sclerosis, atherosclerosis, Alzheimer's disease, septic shock e.g. as anti-hypovolemic and/or anti-hypotensive agents, cerebral edema, headache, migraine, closed head trauma, irritable bowel syndrome and nephritis by the administration of a tablet, cachet, or capsule each containing, for example, 0.1mg, 0.5mg, 1mg, 3mg, 5mg, 10mg, 25mg, 50mg, 100mg, 125mg, 250mg, or 500mg of a compound of this invention once every three to four hours, once, twice or three times a day, or (in an extended release formulation) once, twice or three times a week.

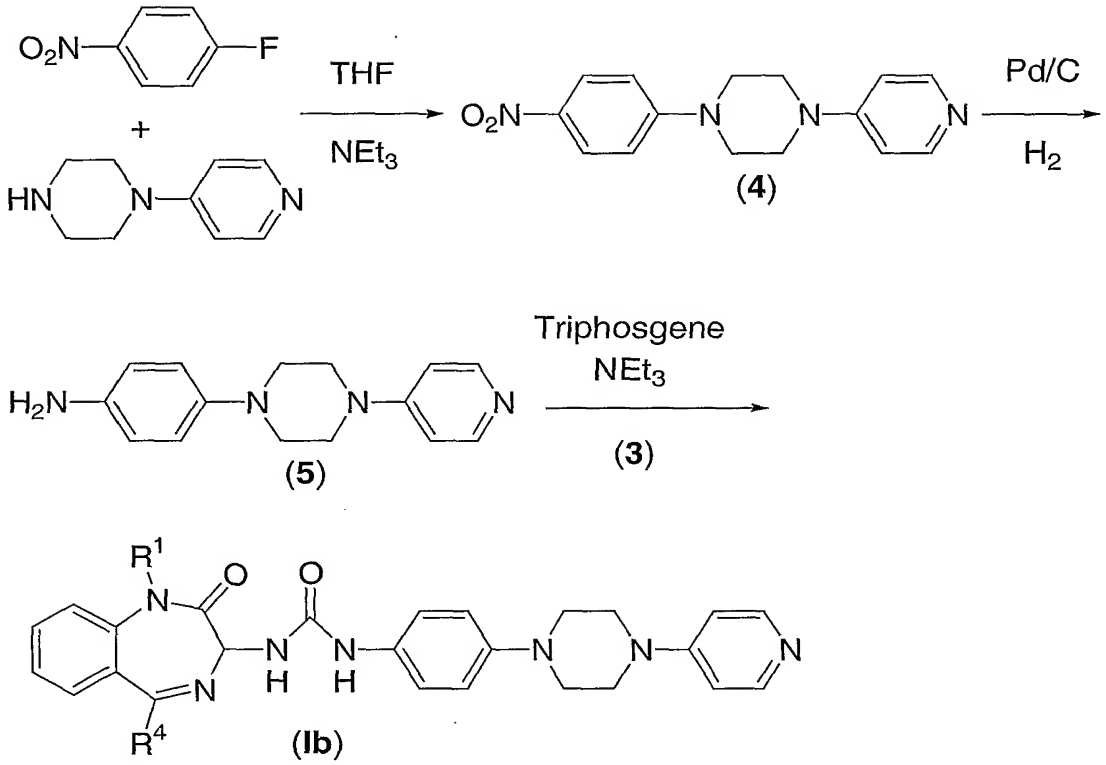
Compounds of the present invention may be prepared as illustrated in the following schemes:

Scheme 1



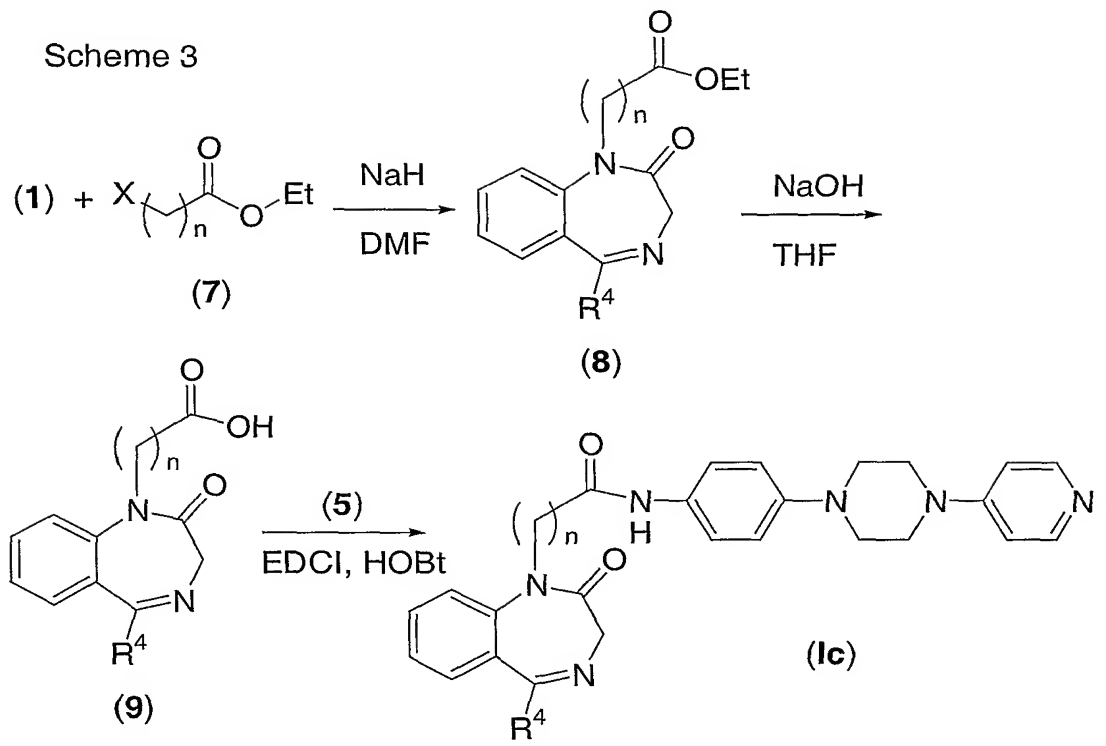
In Scheme 1, the benzodiazepine core (1), obtained commercially or prepared according to *J. Org. Chem.*, 52:3232-3239(1987), is alkylated with an appropriate alkylating agent, like propyl iodide, in an aprotic solvent, like DMF, using a base, like sodium hydride, to provide (2). Compound (2) can then be converted into the 3-amino-benzodiazapine (3) in accordance with *J. Org. Chem.*, 52:3232-3239 (1987). This amine derivative (3) is then reacted with a carboxylic acid or carboxylic acid equivalent, using an appropriate set of peptide coupling reagents, like EDCI/HOBt, in and appropriate solvent, like DMF to yield title compounds (Ia).

Scheme 2



Alternatively, as illustrated in Scheme 2, an amine, like 1-pyridin-4-ylpiperazine, is reacted with 1-fluoro-4-nitrobenzene in an appropriate solvent, like THF, in the presence of a base, like triethylamine, to provide adduct (4). This nitroaromatic intermediate (4) is then reduced to the aniline (5) using standard catalytic hydrogenation conditions, with palladium on carbon in a suitable solvent, like methanol. A urea linkage between aniline (5) and 3-amino-benzodiazapine (3), prepared according to Scheme 1, can be formed using standard conditions, such as triphosgene and triethylamine in THF to provide title compounds (Ib).

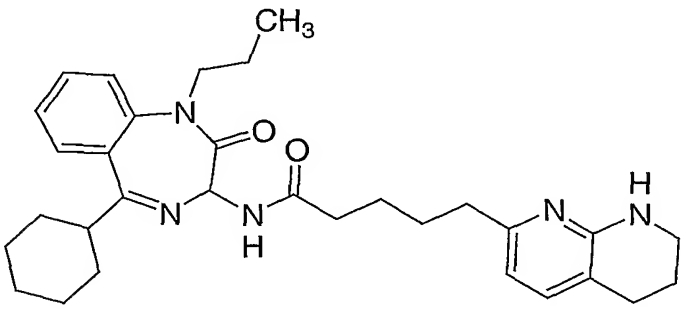
Scheme 3



Alternatively, as illustrated in Scheme 3, the benzodiazepine (1), prepared according to Scheme 1, is alkylated with an ester-containing alkylhalide (7), using a strong base, like sodium hydride, in an aprotic solvent, like DMF, to provide ester (8). This ester (8) is then hydrolyzed by the action of an appropriate base, like sodium hydroxide, in a mixture of water and an organic solvent, like THF, to provide carboxylic acid (9), after acidification. Carboxylic acid (9) is then coupled to the amine (5), prepared according to Scheme 2, using an appropriate set of peptide coupling reagents, like EDCI/HOBt, in and appropriate solvent, like DMF, to provide title compounds (Ic).

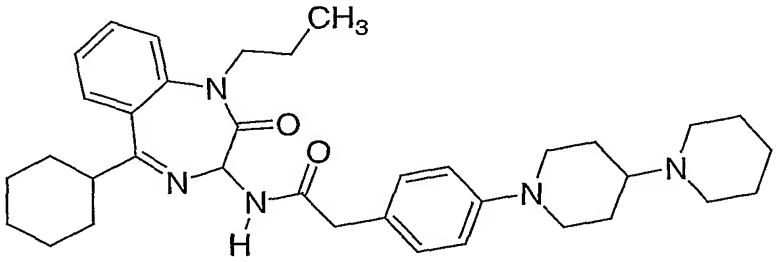
The following examples are provided to illustrate the invention and are not to be construed as limiting the scope thereof in any manner. Compounds were named using: ACD/Name version 4.53 (Advanced Chemistry Development Inc. © 1994-2000). Address: 90 Adelaide Street West, Toronto, Ontario, M5H 3V9, Canada.

EXAMPLE 1: N-(5-cyclohexyl-2-oxo-1-propyl-2,3-dihydro-1H-1,4-benzodiazepin-3-yl)-5-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)pentanamide



The title compound was prepared by the acylation of the 3-amino benzodiazepine core, according to *J. Med. Chem.*, 31:2235-2246(1988), with the carboxylic acid prepared according to International Patent Publication No. WO 9931061. The benzodiazepine portion was either prepared according to *J. Org. Chem.*, 52:3232-3239(1987) or obtained commercially and alkylated at the N-1 position with the appropriate electrophile (in this example, propyl iodide) in DMF using sodium hydride as the base, applying conventional procedures as known in the art. The compound thus obtained gave proton NMR spectra consistent with theory and a mass ion (ES+) of 516.3 for $M+H^+$.

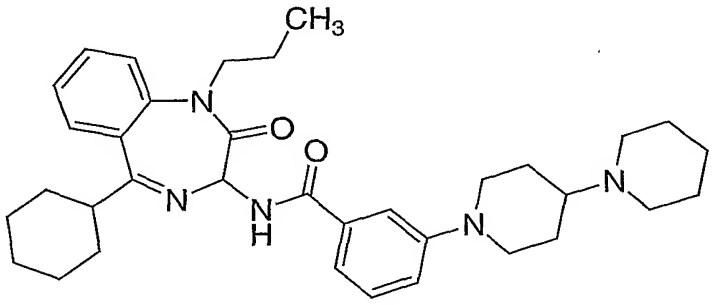
EXAMPLE 2: 2-[4-(1,4'-bipiperidin-1'-yl)phenyl]-N-(5-cyclohexyl-2-oxo-1-propyl-2,3-dihydro-1H-1,4-benzodiazepin-3-yl)acetamide



The title compound was prepared according to the general method of **Example 1**, with the exception that the acyl side chain, (4-[1,4']Bipiperidinyl-1'-yl-phenyl)-acetic acid, was prepared starting from ethyl (4-aminophenyl)acetate. This starting aniline was homologated to the ketone, ethyl [4-(4-oxopiperidin-1-yl)phenyl]-

acetate, according to *Org. Lett.*, 1:1261-1262(1999). The ketone was then reductively aminated with piperidine using Pd/C and hydrogen to provide the required ester, which was hydrolyzed under basic conditions to (4-[1,4']Bipiperidinyl-1'-yl-phenyl)-acetic acid. The title compound gave proton NMR spectra consistent with theory and a mass ion (ES+) of 584.5 for M+H+.

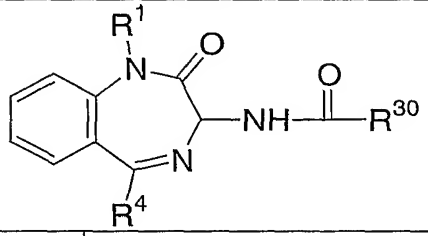
EXAMPLE 3: 3-(1,4'-bipiperidin-1'-yl)-N-(5-cyclohexyl-2-oxo-1-propyl-2,3-dihydro-1H-1,4-benzodiazepin-3-yl)benzamide



The title compound was prepared similarly to **Example 2**, with the exception that the acyl side chain, 3-[1,4']bipiperidinyl-1'-yl-benzoic acid, was prepared using ethyl 3-aminobenzoate instead of ethyl (4-aminophenyl)acetate. The title compound gave proton NMR spectra consistent with theory and a mass ion (ES+) of 570.4 for M+H+.

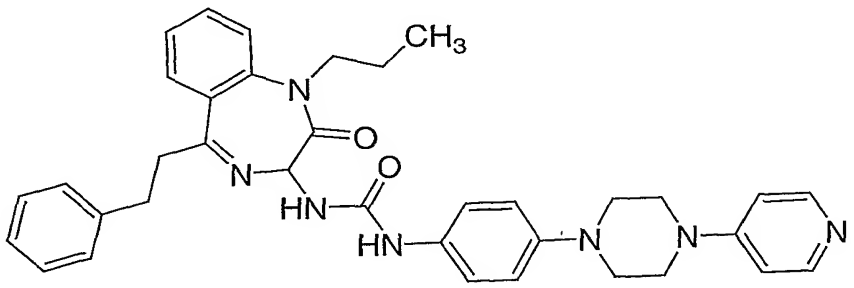
The following compounds in Table 1 were prepared analogously to **Example 1** using commercially available carboxylic acids and acid chlorides for the introduction of R^{30}.

Table 1



Example	R^1	R^{30}	R^4
1.1	Methyl	4-pentylphenyl	phenyl
1.2	Methyl	4-pentylphenyl	2-fluorophenyl
1.3	Isopropyl	3-bromophenyl	phenyl
1.4	Isopropyl	3-(trifluoromethyl)benzyl	phenyl
1.5	H	2-phenoxybenzyl	cyclohexyl
1.6	H	3-methyl-1*H*-inden-2-yl	2-fluorophenyl
1.7	H	Phenyl	2-fluorophenyl
1.8	Methyl	Cyclohexyl	phenyl
1.9	Propyl	4-(dimethylamino)phenyl	cyclohexyl
1.10	Propyl	1*H*-indol-5-yl	cyclohexyl

EXAMPLE 4: N-[2-oxo-5-(2-phenylethyl)-1-propyl-2,3-dihydro-1H-1,4-benzodiazepin-3-yl]-N'-[4-(4-pyridin-4-ylpiperazin-1-yl)phenyl]urea

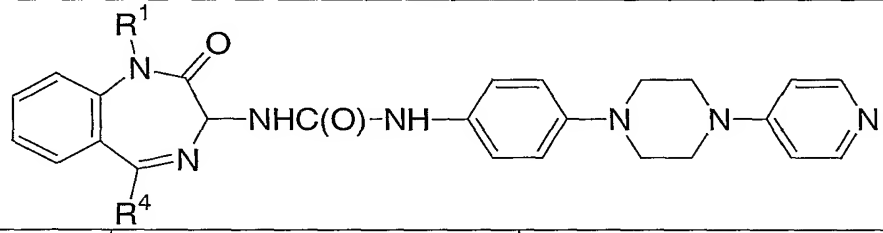


The title compound was prepared by formation of the urea between the benzodiazepine core, 3-amino-5-(2-phenylethyl)-1-propyl-1,3-dihydro-2H-1,4-benzodiazepin-2-one, and the amine side chain, 4-(4-pyridin-4-ylpiperazin-1-yl)aniline, according to *J. Med. Chem.*, 36:4276-4292(1993). The benzodiazepine portion was prepared in accordance with *J. Org. Chem.*, 52:3232-3239(1987). The

amine portion was prepared in accordance with *Tetrahedron Lett.*, 39:2471-2474(1998) starting with 4-fluoronitrobenzene and 1-pyridin-4-yl-piperazine, followed by palladium catalyzed hydrogenation of the nitro group with Pd/C in ethanol, applying conventional procedures as known in the art. **Example 4** thus obtained gave proton NMR spectra consistent with theory and a mass ion (FT/ICR+) of 602.3 for M+H+. While this racemate was potent in biological assays, it could be separated by chiral HPLC methods (*BioMed. Chem. Lett.*, 3:1919-1924(1993)) to provide two enantiomers, both potent, with the preferred enantiomer having an optical rotation of +7.85 ° (c=1, in DCM).

The following compounds in Table 2 were prepared analogously to **Example 4**.

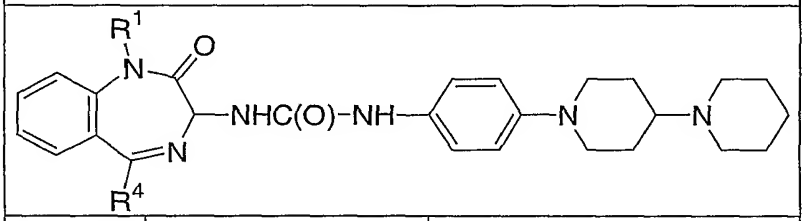
Table 2



Example	R^1	R^4
2.1	Isopropyl	Phenyl
2.2	Propyl	Cyclohexyl
2.3	Cyclopropylmethyl	Cyclohexyl
2.4	Butyl	Cyclohexyl
2.5	Isobutyl	Cyclohexyl
2.6	2,2,2-trifluoroethyl	Cyclohexyl

The following compounds in Table 3 were prepared analogously to **Example 4**, using 1,4'-bipiperidine instead of 1-pyridin-4-yl-piperazine.

Table 3

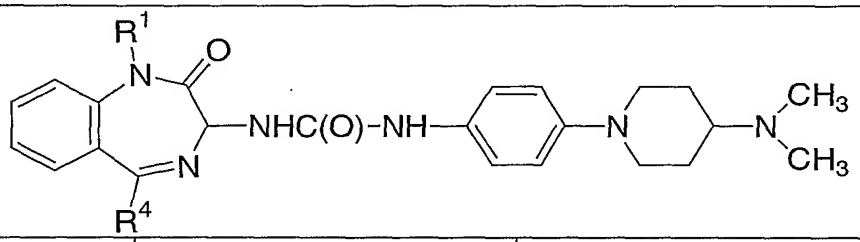


Example	R^1	R^4
3.1	Isopropyl	phenyl
3.2	Cyclopropylmethyl	Cyclohexyl
3.3	Methyl	phenyl
3.4	Propyl	Cyclohexyl
3.5	Propyl	isopropyl
3.6	H	cyclohexyl
3.7	Propyl	tert-butyl
3.8	Propyl	methyl
3.9	Propyl	2-phenylethyl
3.10	Butyl	cyclohexyl
3.11	Isobutyl	cyclohexyl
3.12	Propyl	4-tert-butylcyclohexyl
3.13	Propyl	3,5-dimethylcyclohexyl
3.14	2,2,2-trifluoroethyl	cyclohexyl
3.15	Propyl	4-methylphenyl
3.16	Propyl	3-butenyl
3.17	Propyl	butyl

The following compounds in Table 4 were prepared analogously to **Example 4**, using *N,N*-dimethylpiperidin-4-amine instead of 1-pyridin-4-yl-piperazine.

5

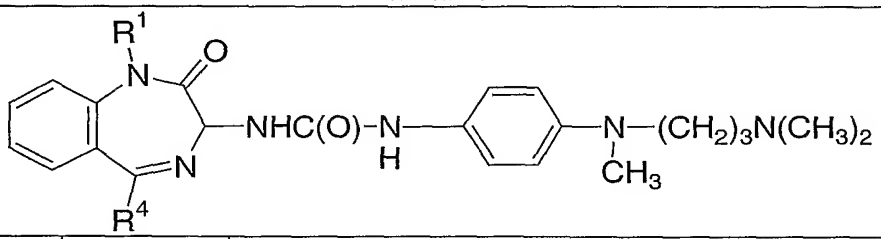
Table 4



Example	R^1	R^4
4.1	Propyl	Cyclohexyl
4.2	Isopropyl	Phenyl
4.3	Cyclopropylmethyl	Cyclohexyl
4.4	Ethyl	Phenyl
4.5	Methyl	Phenyl
4.6	Benzyl	Cyclohexyl

The following compounds in Table 5 were prepared analogously to **Example 4**, using *N,N,N'*-trimethylpropane-1,3-diamine instead of 1-pyridin-4-yl-piperazine.

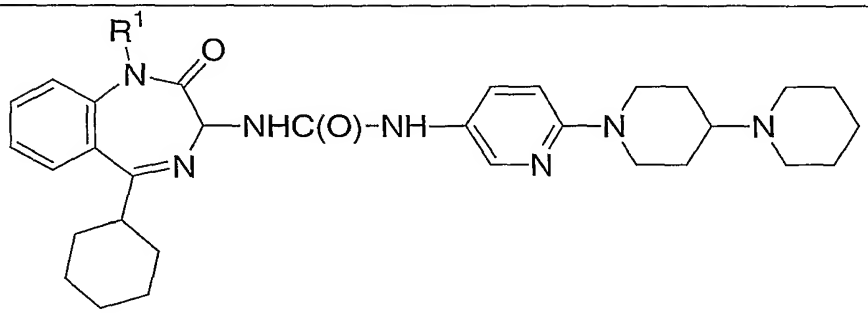
Table 5



Example	R^1	R^4
5.1	Isopropyl	Phenyl
5.2	Propyl	Isopropyl
5.3	Propyl	Cyclohexyl

The following compounds in Table 6 were prepared analogously to **Example 4**, using 1,4'-bipiperidine instead of 1-pyridin-4-yl-piperazine, and 2-chloro-5-nitropyridine instead of 4-fluoronitrobenzene.

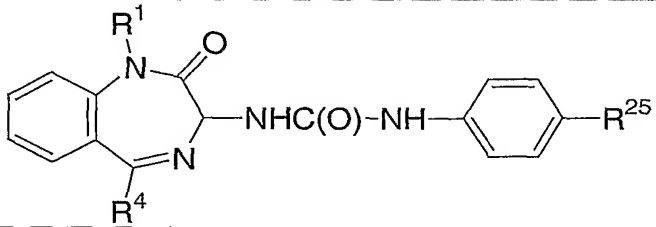
Table 6



Example	R^1
6.1	Propyl
6.2	Cyclopropylmethyl
6.3	Butyl
6.4	Isobutyl

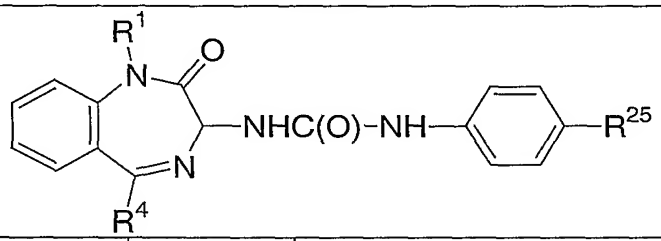
The following compounds in Table 7 where R^{25} is a commercially available nucleophile introduced in accordance with **Example 4** by its reaction with 4-fluoronitrobenzene under basic conditions, applying conventional procedures as known in the art.

Table 7



Example	R^1	R^4	R^{25}
7.1	isopropyl	Phenyl	4-(ethoxycarbonyl)piperidin-1-yl
7.2	propyl	Isopropyl	4-pyrrolidin-1-ylpiperidin-1-yl
7.3	propyl	Cyclohexyl	4-pyrrolidin-1-ylpiperidin-1-yl
7.4	propyl	Cyclohexyl	4-hydroxypiperidin-1-yl
7.5	propyl	Cyclohexyl	4-phenylpiperidin-1-yl
7.6	propyl	Cyclohexyl	2-piperidin-1-ylethoxy
7.7	propyl	Cyclohexyl	4-(ethoxycarbonyl)piperidin-1-yl
7.8	propyl	Cyclohexyl	4-phenylpiperazin-1-yl

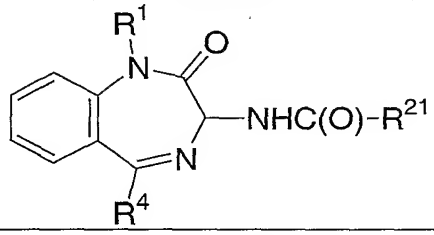
Table 7



Example	R^1	R^4	R^{25}
7.9	propyl	Cyclohexyl	4-(2-oxopyrrolidin-1-yl)piperidin-1-yl
7.10	propyl	Cyclohexyl	4-benzylpiperazin-1-yl
7.11	propyl	Cyclohexyl	4-pyridin-2-ylpiperazin-1-yl

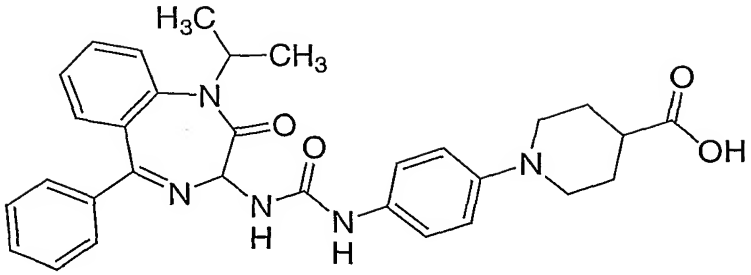
The following compounds in Table 8 were prepared analogously to **Example 4** using commercially available amines for the introduction of R^{21}.

Table 8



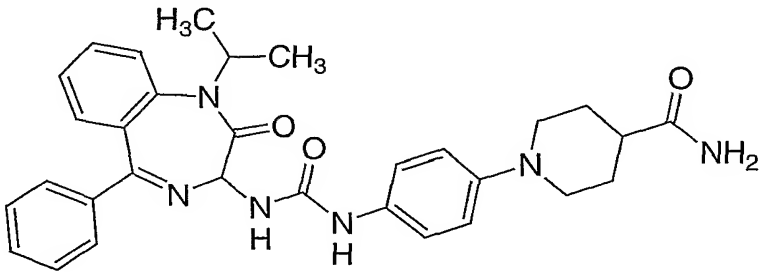
Example	R^1	R^{21}	R^4
8.1	ethyl	(3-methoxyphenyl)amino	phenyl
8.2	propyl	(4-morpholin-4-ylphenyl)amino	isopropyl
8.3	propyl	(4-morpholin-4-ylphenyl)amino	cyclohexyl
8.4	propyl	(4-piperidin-1-ylphenyl)amino	cyclohexyl
8.5	propyl	Pyridin-3-ylamino	cyclohexyl

EXAMPLE 10: 1-[4-({[(1-isopropyl-2-oxo-5-phenyl-2,3-dihydro-1H-1,4-benzodiazepin-3-yl)amino]carbonyl}amino)phenyl]piperidine-4-carboxylic acid



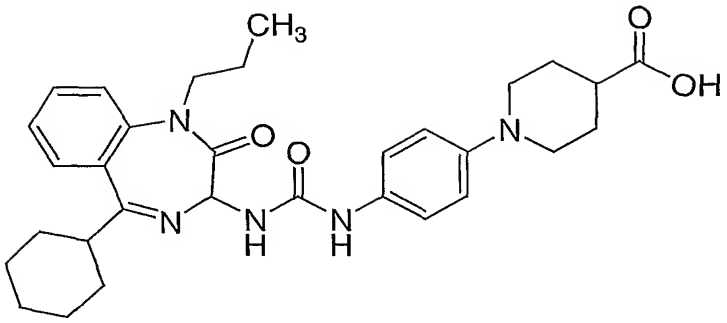
The title compound was prepared by the alkaline hydrolysis of **Example 7.1** in an ethanol/water mixture with sodium hydroxide, applying conventional procedures as known in the art. The compound thus obtained gave proton NMR spectra consistent with theory and a mass ion (FT/ICR+) of 540.3 for M+H+.

EXAMPLE 11: 1-[4-({[(1-isopropyl-2-oxo-5-phenyl-2,3-dihydro-1H-1,4-benzodiazepin-3-yl)amino]carbonyl}amino)phenyl]piperidine-4-carboxamide



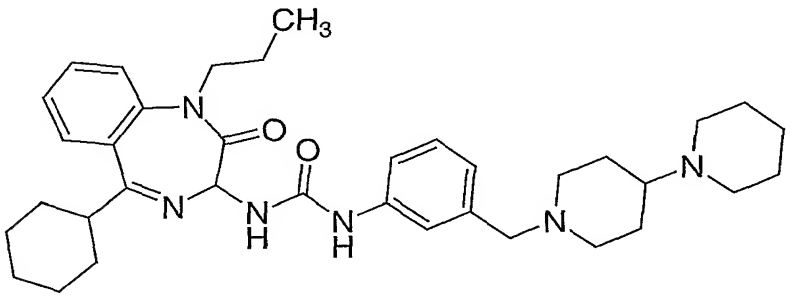
The title compound was prepared by standard peptide coupling conditions using isobutyl chloroformate/triethylamine/ammonia, using **Example 10** as the starting material. The compound thus obtained gave proton NMR spectra consistent with theory and a mass ion (FT/ICR+) of 539.3 for M+H+.

EXAMPLE 12: 1-[4-({[(5-cyclohexyl-2-oxo-1-propyl-2,3-dihydro-1H-1,4-benzodiazepin-3-yl)amino]carbonyl}amino)phenyl]piperidine-4-carboxylic acid



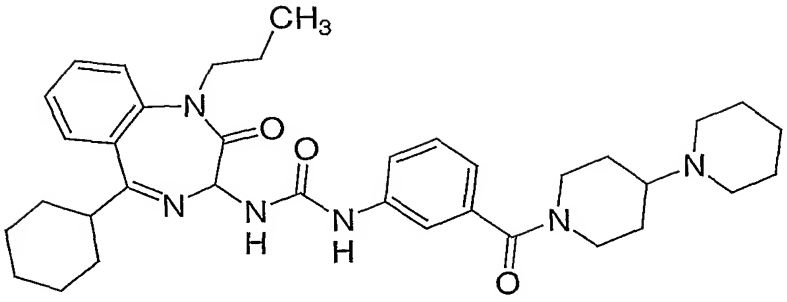
The title compound was prepared by analogy to **Example 10**, using **Example 7.7** as starting material. The compound thus obtained gave proton NMR spectra consistent with theory and a mass ion (FT/ICR+) of 546.3 for M+H+.

EXAMPLE 13: N-[3-(1,4'-bipiperidin-1'-ylmethyl)phenyl]-N'-(5-cyclohexyl-2-oxo-1-propyl-2,3-dihydro-1H-1,4-benzodiazepin-3-yl)urea



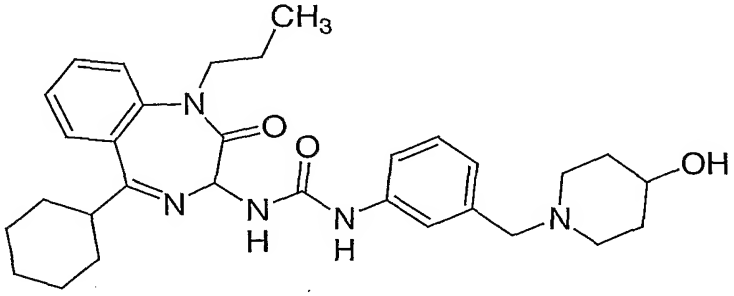
The title compound was prepared by analogy to **Example 4** after the preparation of 3-(1,4'-bipiperidin-1'-ylmethyl)aniline. This aniline was prepared in two steps from 3-nitrobenzyl bromide and 1,4'-bipiperidine. The title compound thus obtained gave proton NMR spectra consistent with theory and a mass ion (FT/ICR+) of 599.4 for M+H+.

EXAMPLE 14: N-[3-(1,4'-bipiperidin-1'-ylcarbonyl)phenyl]-N'-(5-cyclohexyl-2-oxo-1-propyl-2,3-dihydro-1H-1,4-benzodiazepin-3-yl)urea



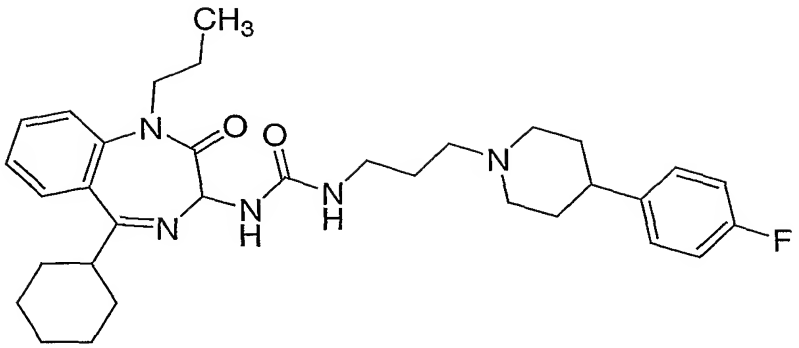
The title compound was prepared by analogy to **Example 13** employing 3-nitrobenzoyl chloride rather than 3-nitrobenzyl bromide. The final compound thus obtained gave proton NMR spectra consistent with theory and a mass ion (ES+) of 613.4 for M+H+.

EXAMPLE 15: N-(5-cyclohexyl-2-oxo-1-propyl-2,3-dihydro-1H-1,4-benzodiazepin-3-yl)-N'-{3-[(4-hydroxypiperidin-1-yl)methyl]phenyl}urea



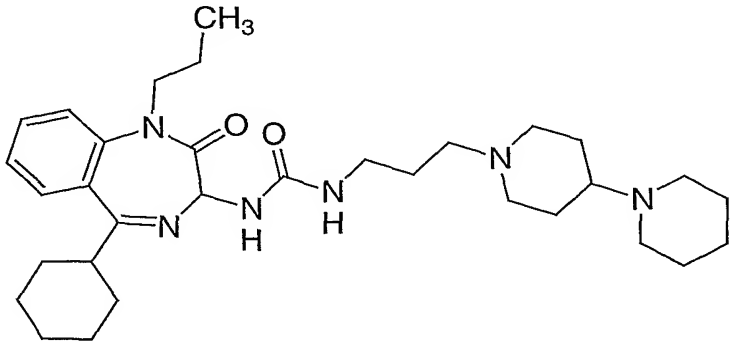
The title compound was prepared by analogy to **Example 13** employing 4-hydroxypiperidine rather than 1,4'-bipiperidine. The final compound thus obtained gave proton NMR spectra consistent with theory and a mass ion (ES+) of 532.3 for M+H+.

EXAMPLE 16: N-(5-cyclohexyl-2-oxo-1-propyl-2,3-dihydro-1H-1,4-benzodiazepin-3-yl)-N'-{3-[4-(4-fluorophenyl)piperidin-1-yl]propyl}urea



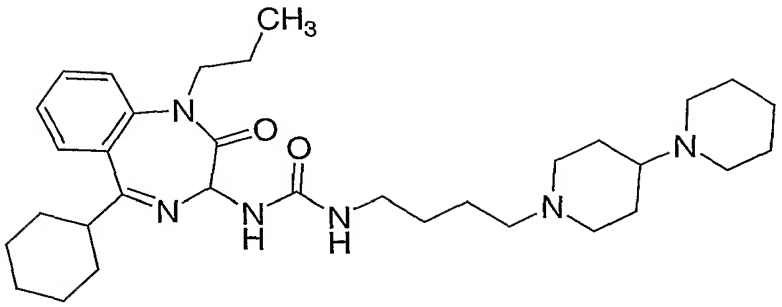
The title compound was prepared by analogy to **Example 4** after the preparation of 3-[4-(4-fluorophenyl)piperidin-1-yl]propan-1-amine. This amine was prepared in two steps from 2-(3-bromopropyl)-1H-isoindole-1,3(2H)-dione and 4-(4-fluorophenyl)piperidine. The title compound thus obtained gave proton NMR spectra consistent with theory and a mass ion (ES+) of 562.4 for M+H+.

EXAMPLE 17: N-[3-(1,4'-bipiperidin-1'-yl)propyl]-N'-(5-cyclohexyl-2-oxo-1-propyl-2,3-dihydro-1H-1,4-benzodiazepin-3-yl)urea



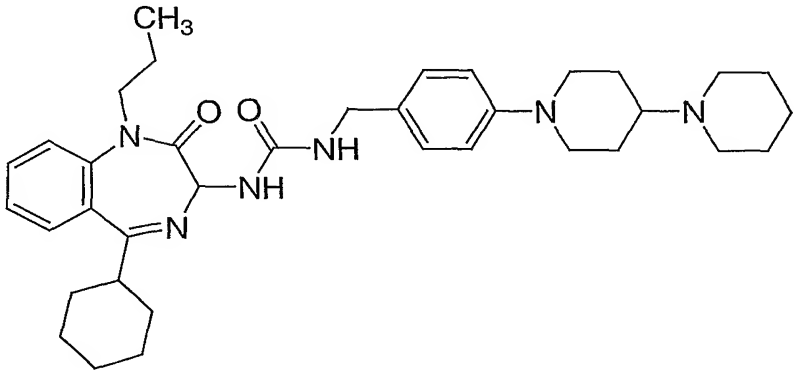
The title compound was prepared by analogy to **Example 4** after the preparation of 3-(1,4'-bipiperidin-1'-yl)propan-1-amine. This amine was prepared in two steps from 2-(3-bromopropyl)-1H-isoindole-1,3(2H)-dione and 1,4'-bipiperidine. The title compound thus obtained gave proton NMR spectra consistent with theory and a mass ion (ES+) of 551.5 for M+H+.

EXAMPLE 18: N-[4-(1,4'-bipiperidin-1'-yl)butyl]-N'-(5-cyclohexyl-2-oxo-1-propyl-2,3-dihydro-1H-1,4-benzodiazepin-3-yl)urea



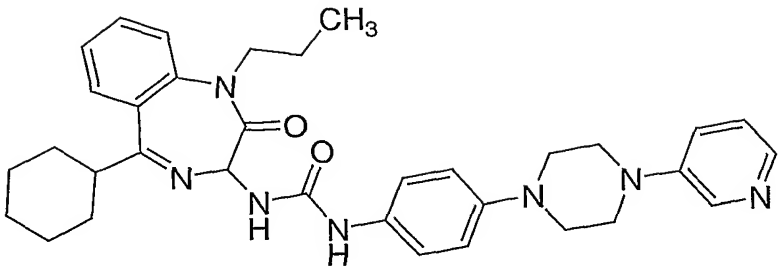
The title compound was prepared by analogy to **Example 17** using 2-(4-bromobutyl)-1H-isoindole-1,3(2H)-dione instead of using 2-(3-bromopropyl)-1H-isoindole-1,3(2H)-dione. The title compound thus obtained gave proton NMR spectra consistent with theory and a mass ion (ES+) of 565.4 for M+H+.

EXAMPLE 19: N-[4-(1,4'-bipiperidin-1'-yl)benzyl]-N'-(5-cyclohexyl-2-oxo-1-propyl-2,3-dihydro-1H-1,4-benzodiazepin-3-yl)urea



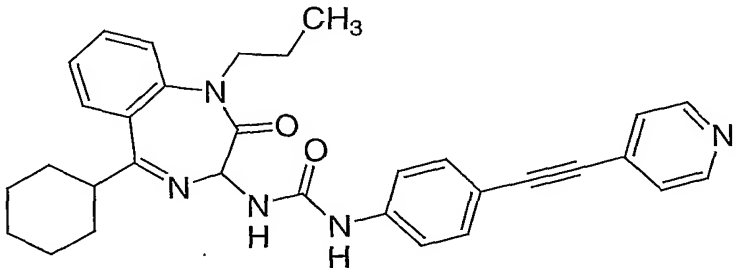
The title compound was prepared by analogy to **Example 4** after the preparation of 1-[4-(1,4'-bipiperidin-1'-yl)phenyl]methanamine. This amine was prepared in two steps from 4-fluorobenzonitrile and 1,4'-bipiperidine. The title compound thus obtained gave proton NMR spectra consistent with theory and a mass ion (ES+) of 599.4 for M+H+.

EXAMPLE 20: N-(5-cyclohexyl-2-oxo-1-propyl-2,3-dihydro-1H-1,4-benzodiazepin-3-yl)-N'-[4-(4-pyridin-3-ylpiperazin-1-yl)phenyl]urea



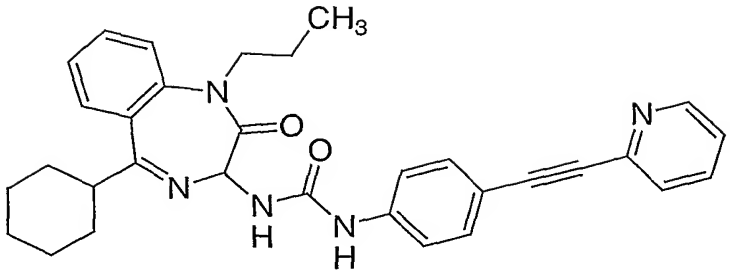
The title compound was prepared by analogy to **Example 4** after the preparation of 1-pyridin-3-ylpiperazine. This piperazine was prepared according to *Tetrahedron Lett.*, 39:617-620(1998). The title compound thus obtained gave proton NMR spectra consistent with theory and a mass ion (ES+) of 580.3 for M+H+.

EXAMPLE 21: N-(5-cyclohexyl-2-oxo-1-propyl-2,3-dihydro-1H-1,4-benzodiazepin-3-yl)-N'-[4-(pyridin-4-ylethynyl)phenyl]urea



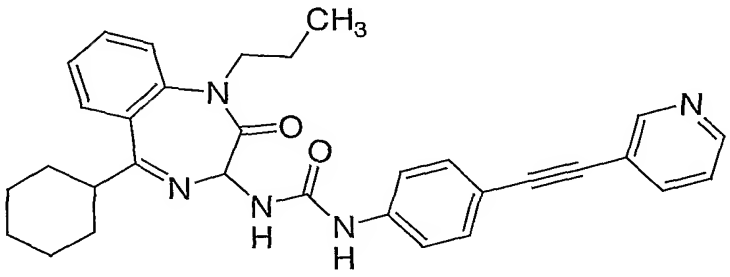
The title compound was prepared by analogy to **Example 4** after the preparation of 4-(pyridin-4-ylethynyl)aniline. This aniline was prepared in one step from 4-bromopyridine and 4-ethynylaniline according to *Acta. Chem. Scand., Ser B*, 42:448(1988). The title compound thus obtained gave proton NMR spectra consistent with theory and a mass ion (ES+) of 520.3 for M+H+.

EXAMPLE 22: N-(5-cyclohexyl-2-oxo-1-propyl-2,3-dihydro-1H-1,4-benzodiazepin-3-yl)-N'-[4-(pyridin-2-ylethynyl)phenyl]urea



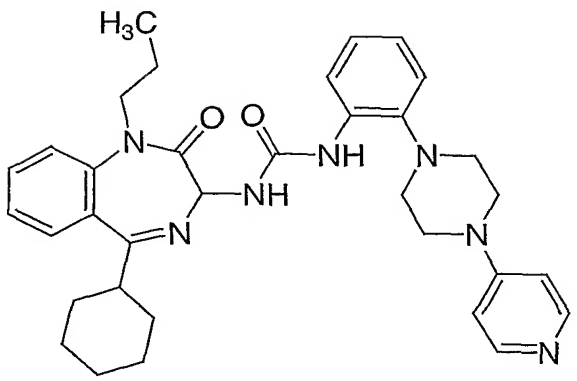
The title compound was prepared by analogy to **Example 21**, using 2-bromopyridine instead of 4-bromopyridine. The title compound thus obtained gave proton NMR spectra consistent with theory and a mass ion (ES+) of 520.2 for M+H+.

EXAMPLE 23: N-(5-cyclohexyl-2-oxo-1-propyl-2,3-dihydro-1H-1,4-benzodiazepin-3-yl)-N'-[4-(pyridin-3-ylethynyl)phenyl]urea



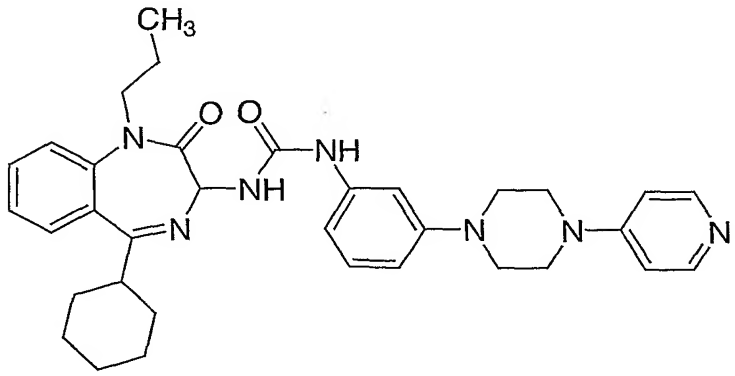
The title compound was prepared by analogy to **Example 21**, using 3-bromopyridine instead of 4-bromopyridine. The title compound thus obtained gave proton NMR spectra consistent with theory and a mass ion (ES+) of 520.2 for M+H+.

EXAMPLE 24: N-(5-cyclohexyl-2-oxo-1-propyl-2,3-dihydro-1H-1,4-benzodiazepin-3-yl)-N'-[2-(4-pyridin-4-ylpiperazin-1-yl)phenyl]urea



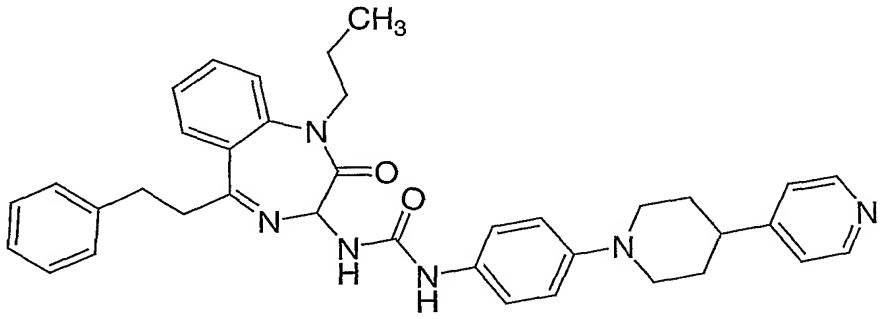
The title compound was prepared by analogy to **Example 4**, using 2-fluoronitrobenzene instead of 4-fluoronitrobenzene. The title compound thus obtained gave proton NMR spectra consistent with theory and a mass ion (FT/ICR+) of 580.3 for M+H+.

EXAMPLE 25: N-(5-cyclohexyl-2-oxo-1-propyl-2,3-dihydro-1H-1,4-benzodiazepin-3-yl)-N'-[3-(4-pyridin-4-ylpiperazin-1-yl)phenyl]urea



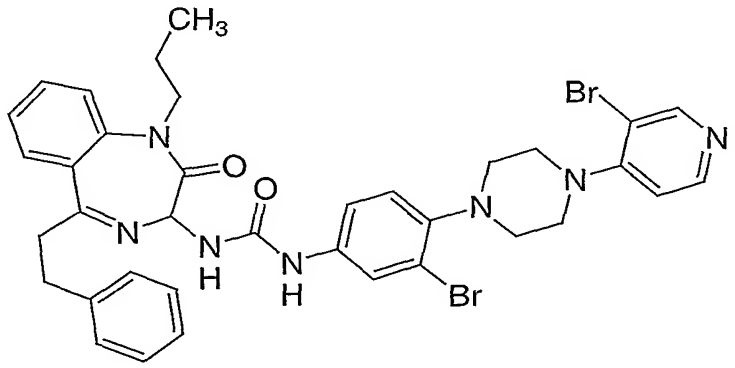
The title compound was prepared by analogy to **Example 4**, after the preparation of 3-(4-pyridin-4-ylpiperazin-1-yl)aniline. This aniline was prepared using 3-fluoronitrobenzene and 1-pyridin-4-ylpiperazine *in* DMSO, *at* 90°C, *for* 60*h* with potassium carbonate; followed by hydrogenation of the nitro group. The title compound thus obtained gave proton NMR spectra consistent with theory and a mass ion (EI+) of 579.4 for M+.

EXAMPLE 26: N-[2-oxo-5-(2-phenylethyl)-1-propyl-2,3-dihydro-1H-1,4-benzodiazepin-3-yl]-N'-[4-(4-pyridin-4-ylpiperidin-1-yl)phenyl]urea



The title compound was prepared by analogy to **Example 4**, after the preparation of 4-piperidin-4-ylpyridine, which was used instead of 1-pyridin-4-ylpiperazine. This pyridine was prepared according to *Tetrahedron Lett.*, 34:5287-5288(1993). The title compound thus obtained gave proton NMR spectra consistent with theory and a mass ion (ES+) of 601.3 for M+H+.

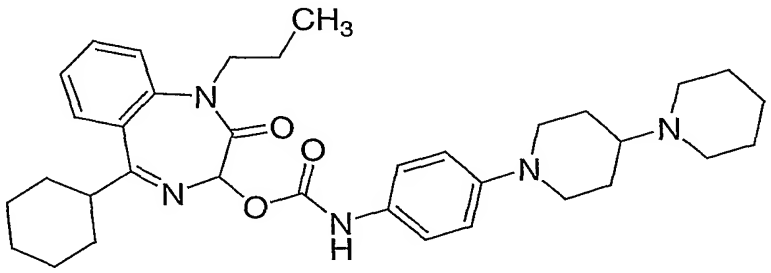
EXAMPLE 27: N-{3-bromo-4-[4-(3-bromopyridin-4-yl)piperazin-1-yl]phenyl}-N'-[2-oxo-5-(2-phenylethyl)-1-propyl-2,3-dihydro-1H-1,4-benzodiazepin-3-yl]urea



The title compound was prepared by analogy to **Example 4**, after the preparation of 3-bromo-4-[4-(3-bromopyridin-4-yl)piperazin-1-yl]aniline. This aniline was prepared in 3 steps from 4-fluoronitrobenzene and 1-pyridin-4-ylpiperazine. After these two starting materials were allowed to react according to

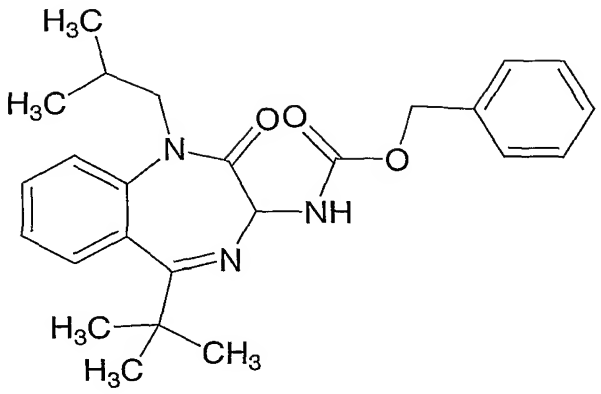
Tetrahedron Lett., 39:2471-2474(1998), the resulting product was bis-brominated with NBS in methylene chloride, and then the nitro group was reduced with iron(0) in acetic acid / ethanol / aqueous HCl, applying conventional procedures as known in the art. The title compound thus obtained gave proton NMR spectra consistent with theory and a mass ion (ES+) of 757.8 for M+H+($^{79}Br_2$).

EXAMPLE 28: 5-cyclohexyl-2-oxo-1-propyl-2,3-dihydro-1H-1,4-benzodiazepin-3-yl 4-(1,4'-bipiperidin-1'-yl)phenylcarbamate



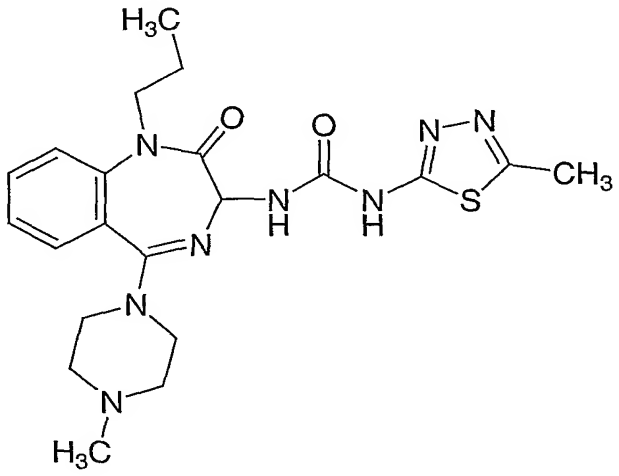
The title compound was prepared by analogy to **Example 3.4**. The benzodiazepine core, 5-cyclohexyl -1-propyl-1,3-dihydro-2H-1,4-benzodiazepin-2-one, was prepared according to *J.O.C.*, 52:3232-3239(1987). This benzodiazepine was then oxidized at N-4 with *m*CPBA, rearranged to the C-3 acetate with acetic anhydride at 100°C, and then hydrolyzed to the C-3 hydroxyl. This was then coupled to the aniline used in Table 3. The title compound thus obtained gave proton NMR spectra consistent with theory and a mass ion (FT/ICR+) of 293.7 for M+2H+.

EXAMPLE 29: benzyl 5-tert-butyl-1-isobutyl-2-oxo-2,3-dihydro-1H-1,4-benzodiazepin-3-ylcarbamate



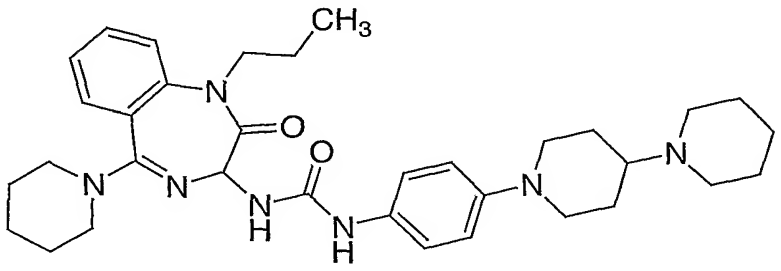
The title compound was prepared according to *J. Med. Chem.*, 36:4276-4292(1993), using 1-(2-aminophenyl)-2,2-dimethylpropan-1-one and {[(benzyloxy)carbonyl]amino}[(tert-butoxycarbonyl)amino]acetic acid as starting materials.

EXAMPLE 30: N-[5-(4-methylpiperazin-1-yl)-2-oxo-1-propyl-2,3-dihydro-1H-1,4-benzodiazepin-3-yl]-N'-(5-methyl-1,3,4-thiadiazol-2-yl)urea



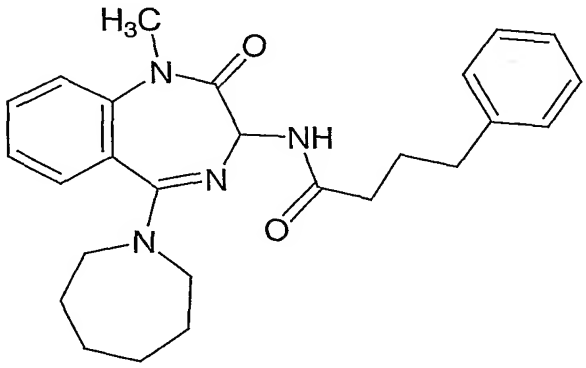
The title compound was prepared by analogy to **Example 4**, after the preparation of 3-amino-5-(4-methylpiperazin-1-yl)-1-propyl-1,3-dihydro-2H-1,4-benzodiazepin-2-onedine, which was prepared according to *J. Med. Chem.*, 37:719-721(1994).

EXAMPLE 31: N-[4-(1,4'-bipiperidin-1'-yl)phenyl]-N'-(2-oxo-5-piperidin-1-yl-1-propyl-2,3-dihydro-1H-1,4-benzodiazepin-3-yl)urea



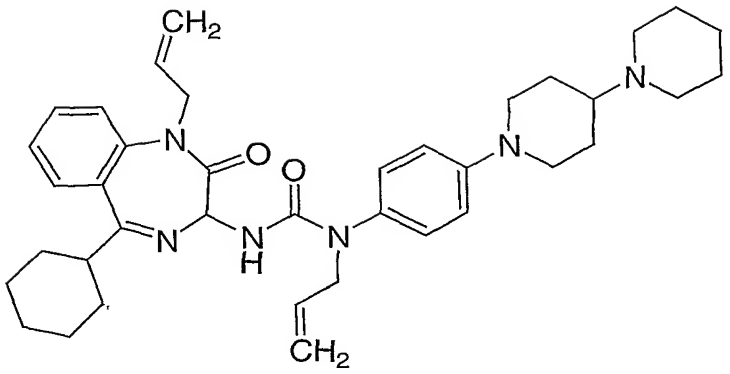
The title compound was prepared by analogy to **Example 30**, using the aniline of **Example 3.1**, after the preparation of 3-amino-5-piperidin-1-yl-1-propyl-1,3-dihydro-2H-1,4-benzodiazepin-2-one, which was prepared according to *J. Med. Chem.*, 37:719-721(1994). The title compound thus obtained gave proton NMR spectra consistent with theory and a mass ion (FAB+) of 586.4 for M+H+.

EXAMPLE 32: N-(5-azepan-1-yl-1-methyl-2-oxo-2,3-dihydro-1H-1,4-benzodiazepin-3-yl)-4-phenylbutanamide



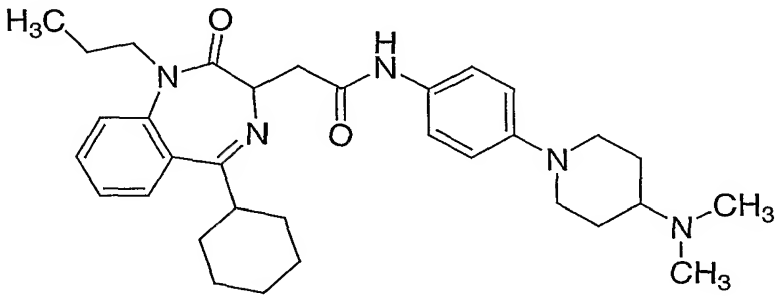
The title compound was prepared by analogy to **Example 1**, after the preparation of 3-amino-5-azepan-1-yl-1-methyl-1,3-dihydro-2H-1,4-benzodiazepin-2-one, which was prepared according to *J. Med. Chem.*, 37:719-721(1994).

EXAMPLE 33: N-allyl-N'-(1-allyl-5-cyclohexyl-2-oxo-2,3-dihydro-1H-1,4-benzodiazepin-3-yl)-N-[4-(1,4'-bipiperidin-1'-yl)phenyl]urea



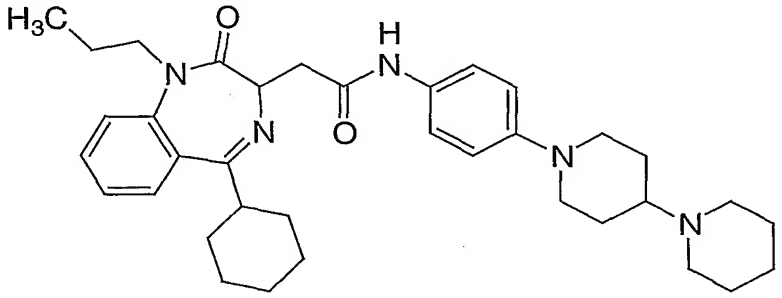
The title compound was prepared by exposing **Example 3.6** to excess allyl bromide and sodium hydride in DMF. The title compound thus obtained gave proton NMR spectra consistent with theory and a mass ion (ES+) of 623.4 for M+H+.

EXAMPLE 34: 2-(5-cyclohexyl-2-oxo-1-propyl-2,3-dihydro-1H-1,4-benzodiazepin-3-yl)-N-{4-[4-(dimethylamino)piperidin-1-yl]phenyl}acetamide



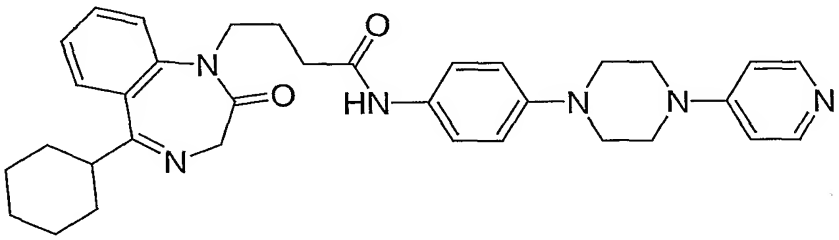
The title compound was prepared from the benzodiazepine core, 5-cyclohexyl-1-propyl-1,3-dihydro-2H-1,4-benzodiazepin-2-one, and the aniline used in Table 4. The benzodiazepine was alkylated at the C-3 position with tert-butyl bromoacetate and potassium tert-butoxide. After aqueous acidic removal of the tert-butyl group, the resulting acid was coupled with 1-(4-aminophenyl)-N,N-dimethylpiperidin-4-amine, employing standard N,N'-dicyclohexylcarbodiimide/N,N-dimethylpyridin-4-amine techniques. The title compound thus obtained gave proton NMR spectra consistent with theory and a mass ion (ES+) of 584.6 for M+H+.

EXAMPLE 35: N-[4-(1,4'-bipiperidin-1'-yl)phenyl]-2-(5-cyclohexyl-2-oxo-1-propyl-2,3-dihydro-1H-1,4-benzodiazepin-3-yl)acetamide



The title compound was prepared by analogy to **Example 36** using 4-(1,4'-bipiperidin-1'-yl)aniline instead of 1-(4-aminophenyl)-N,N-dimethylpiperidin-4-amine. The title compound thus obtained gave proton NMR spectra consistent with theory and a mass ion (ES+) of 544.5 for M+H+.

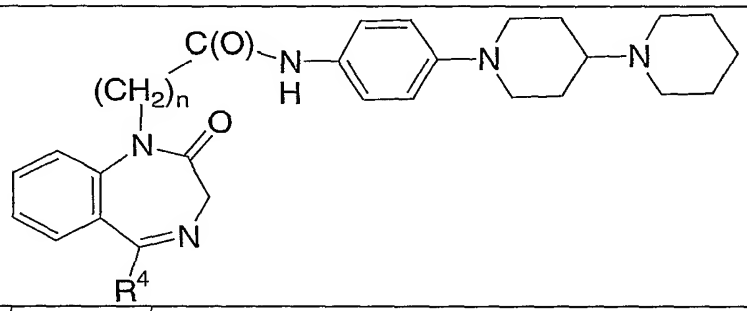
EXAMPLE 36 4-(5-cyclohexyl-2-oxo-2,3-dihydro-1H-1,4-benzodiazepin-1-yl)-N-[4-(4-pyridin-4-ylpiperazin-1-yl)phenyl]butanamide



The title compound was synthesized from the core benzodiazepine, 5-cyclohexyl-1,3-dihydro-2H-1,4-benzodiazepin-2-one, prepared according to *J.O.C.*, 52:3232-3239(1987). This benzodiazepine was alkylated at the N-1 position using ethyl 4-bromobutanoate and sodium hydride. After hydrolysis of the ester using THF/water/NaOH, the resulting acid was coupled with 4-(4-pyridin-4-ylpiperazin-1-yl)aniline, described in **Example 4**, using standard EDCI/HOBt techniques. The title compound thus obtained gave proton NMR spectra consistent with theory and a mass ion (FT/ICR+) of 565.3 for M+H+.

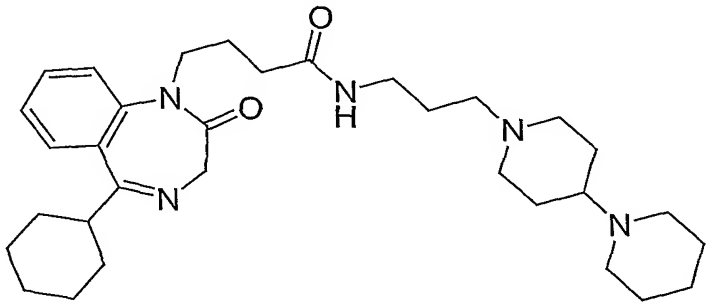
The following compounds in Table 9 were prepared analogously to **Example 37**, using 4-(1,4'-bipiperidin-1'-yl)aniline instead of 4-(4-pyridin-4-ylpiperazin-1-yl)aniline.

Table 9



Example	n	R^4
9.1	1	Cyclohexyl
9.2	2	Cyclohexyl
9.3	3	Cyclohexyl
9.4	4	Cyclohexyl
9.5	5	Cyclohexyl
9.6	3	2-phenylethyl
9.7	3	tert-butyl
9.8	3	Methyl

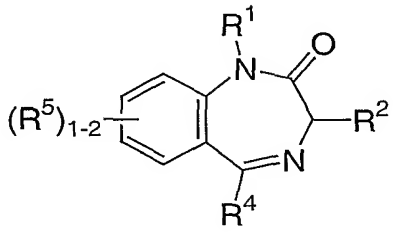
EXAMPLE 37: N-[3-(1,4'-bipiperidin-1'-yl)propyl]-4-(5-cyclohexyl-2-oxo-2,3-dihydro-1H-1,4-benzodiazepin-1-yl)butanamide



The title compound was prepared by analogy to **Example 37** using the amine described in **Example 17**. The title compound thus obtained gave proton NMR spectra consistent with theory and a mass ion (FT/ICR+) of 536.4 for M+H+.

WHAT IS CLAIMED IS:

1. A compound represented by Formula I:



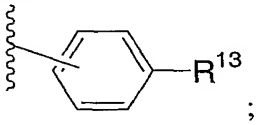
(I)

or a pharmaceutically acceptable salt thereof, wherein:

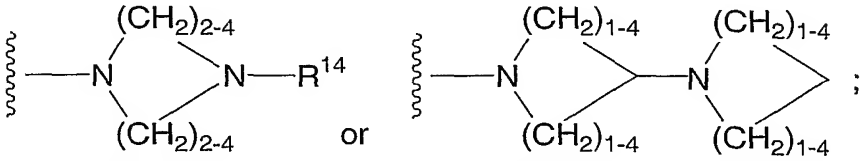
R^1 is H, C_{1-8}alkyl (optionally substituted with 1-9 independent halogens), C_{1-6}alkyloxy–, –C_{1-10}alkylaryl, –C_{0-2}alkyl–C_{3-10}cycloalkyl or C_{2-6}alkenyl;

R^2 is –$NHC(O)NR^{22}R^{23}$, –$OC(O)NR^{22}R^{23}$, –C_{1-3}alkyl-$C(O)NR^{22}R^{23}$ or -$NHC(O)R^{23}$; or

R^2 is H and R^1 is –C_{1-7}alkyl-C(O)-NH-R^{12};

R^{12} is -C_{2-4}alkyl-R^{13} or  ;

R^{13} is



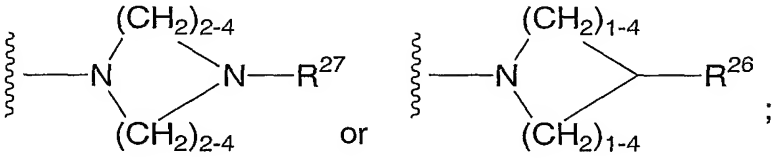
R^{14} is aryl or heteroaryl wherein the aryl or heteroaryl is optionally substituted with 1-2 substituents, each substituent independently is C_{1-6}alkyl, C_{1-6}alkyloxy, C_{1-6}alkylcarboxy-, C_{1-6}alkylamido, OH, halogen, nitro, amino or cyano;

R^{22} is H, C_{1-8}alkyl (optionally substituted with 1-9 independent halogens), C_{1-6}alkyloxy–, –C_{1-10}alkylaryl, –C_{0-2}alkyl–C_{3-10}cycloalkyl, or C_{2-6}alkenyl;

R^{23} is $-C_{2-6}alkyl-R^{25}$, $-C_{1-6}alkyl-R^{31}$, $-C_{0-4}alkylaryl$, or $-C_{0-4}alkylheteroaryl$, wherein the aryl or heteroaryl is substituted with a group selected from $-C\equiv C-R^{44}$, $-(CH_2)_{0-4}-R^{25}$ and $-C(O)-R^{25}$;

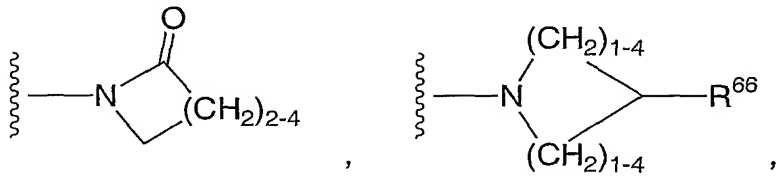
R^{44} is aryl or heteroaryl, wherein the aryl or heteroaryl is optionally substituted with 1-2 substituents, each substituent independently is $C_{1-6}alkyl$ (optionally substituted with 1-9 independent halogens), $C_{1-6}alkyloxy-$, $C_{1-6}alkyl-carboxy-$, $C_{1-6}alkylamido-$, OH, halogen, nitro, amino or cyano;

R^{25} is



;

R^{26} is H, $-NR^{66}R^{67}$, $-C(O)-O-R^{66}$, $-C(O)-NR^{66}R^{67}$, OH,



,

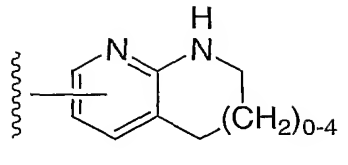
,

aryl or heteroaryl, wherein the aryl or heteroaryl is optionally substituted with 1-2 substituents, each substituent independently is $C_{1-6}alkyl$ (optionally substituted with 1-9 independent halogens), $C_{1-6}alkyloxy-$, $C_{1-6}alkylcarboxy-$, $C_{1-6}alkylamido-$, OH, halogen, nitro, amino, or cyano;

R^{66} and R^{67} are each independently H, OH, $C_{1-8}alkyl$ (optionally substituted with 1-9 independent halogens), $C_{1-6}alkyloxy-$, $-C_{1-10}alkylaryl$, $-C_{0-2}alkyl-C_{3-10}cycloalkyl$, or $C_{2-6}alkenyl$;

R^{27} is $-C_{0-2}alkyl-C_{3-10}cycloalkyl$, $-C_{0-2}alkylaryl$, or $-C_{0-2}alkylheteroaryl$, wherein the aryl or heteroaryl is optionally substituted with 1-2 substituents, each substituent independently is $C_{1-6}alkyl$ (optionally substituted with 1-9 independent halogens), $C_{1-6}alkyloxy-$, $C_{1-6}alkylcarboxy-$, $C_{1-6}alkylamido-$, OH, halogen, nitro, amino or cyano;

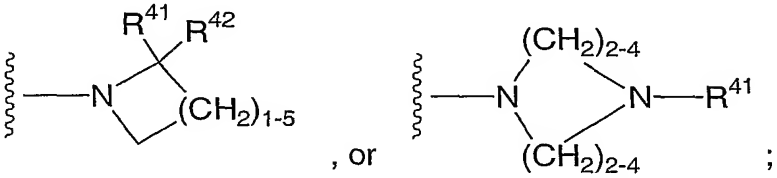
R^{31} is



;

R^4 is C_{1-8}alkyl (optionally substituted with 1-9 independent halogens), C_{1-6}alkyloxy–, –C_{0-3}alkyl–C_{3-10}cycloalkyl, C_{2-8}alkenyl, –C_{0-3}alkylaryl, or –C_{0-3}alkylheteroaryl, wherein the aryl or heteroaryl is optionally substituted with 1-3 substituents, each substituent independently is C_{1-6}alkyl (optionally substituted with 1-9 independent halogens), C_{1-6}alkyloxy–, C_{1-6}alkylcarboxy–, C_{1-6}alkylamido–, OH, halogen, nitro, amino, or cyano, or

R^4 is



;

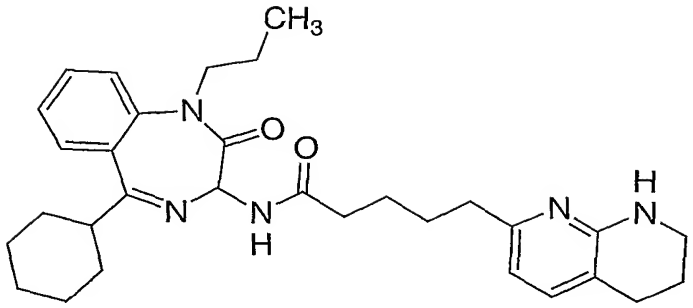
R^{41} and R^{42} are each independently H, C_{1-8}alkyl (optionally substituted with 1-9 independent halogens), C_{1-6}alkyloxy–, –C_{1-10}alkylaryl, -C_{0-2}alkyl–C_{3-10}cycloalkyl, or C_{2-6}alkenyl;

R^5 is H, nitro, halogen, cyano, OH, amino, C_{1-6}alkylthio–, C_{1-8}alkyl (optionally substituted with 1-9 independent halogens), C_{1-8}alkyloxy–, -C_{0-10}alkylaryl, –C_{0-10}alkylheteroaryl, –C(O)–C_{0-2}alkylaryl, -C(O)-C_{0-2}alkylheteroaryl, –C(O)–O–aryl, –C(O)–O–heteroaryl, –C(O)–NH–C_{0-2}alkylaryl, -C(O)–NH–C_{0-2}alkylheteroaryl, –C(O)–N(C_{1-8}alkyl)–C_{0-2}alkylaryl, or -C(O)–N(C_{1-8}alkyl)–C_{0-2}alkylheteroaryl, wherein the aryl or heteroaryl is optionally substituted with 1-2 substituents, each substituent independently is C_{1-6}alkyl, C_{1-6}alkyloxy–, C_{1-6}alkylcarboxy–, C_{1-6}alkylamido–, OH, halogen, nitro, amino, or cyano.

2. The compound according to Claim 1, or a pharmaceutically acceptable salt thereof, wherein

R^2 is –NH–C(O)–C_{1-6}alkyl–R^{31}.

3. The compound according to Claim 2, represented by



or a pharmaceutically acceptable salt thereof.

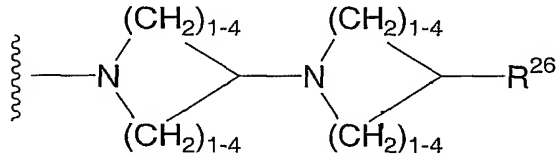
4. The compound according to Claim 1, or a pharmaceutically acceptable salt thereof, wherein

R^2 is $-NH-C(O)-R^{23}$.

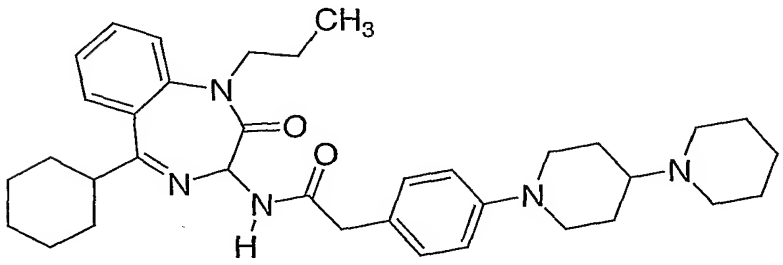
5. The compound according to Claim 4, or a pharmaceutically acceptable salt thereof, wherein

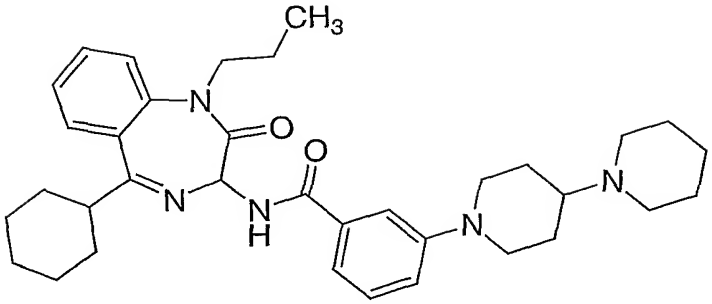
R^{23} is $-C_{0-4}$alkylaryl substituted with $-(CH_2)_{0-4}-R^{25}$;

R^{25} is



6. The compound according to Claim 4 represented by



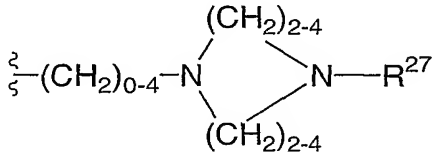


or a pharmaceutically acceptable salt thereof.

7. The compound according to Claim 1, wherein

R^2 is –NH–C(O)–$NR^{22}R^{23}$;

R^{23} is –C_{0-4}alkylaryl, wherein the aryl is substituted with



; and

R^{27} is –C_{0-2}alkylaryl, or –C_{0-2}alkylheteroaryl, wherein the aryl or heteroaryl is optionally substituted with 1-2 substituents, each substituent independently is C_{1-6}alkyl (optionally substituted with 1-9 independent halogens), C_{1-6}alkyloxy–, C_{1-6}alkylcarboxy–, C_{1-6}alkylamido–, OH, halogen, nitro, amino or cyano;

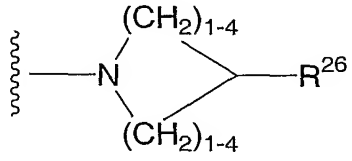
or a pharmaceutically acceptable salt thereof.

8. The compound according to Claim 1, wherein

R^2 is –NH–C(O)–$NR^{22}R^{23}$;

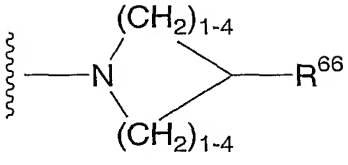
R^{23} is –C_{0-4}alkylaryl, wherein the aryl is substituted with -$(CH_2)_{0-4}$-R^{25}, or –C(O)–R^{25};

R^{25} is



; and

R^{26} is



;

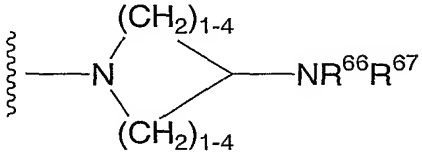
or a pharmaceutically acceptable salt thereof.

9. The compound according to Claim 1, wherein

R^2 is –NH–C(O)–$NR^{22}R^{23}$;

R^{23} is –C_{0-4}alkylaryl, wherein the aryl is substituted with –$(CH_2)_{0-4}$–R^{25}, or –C(O)–R^{25};

R^{25} is



;

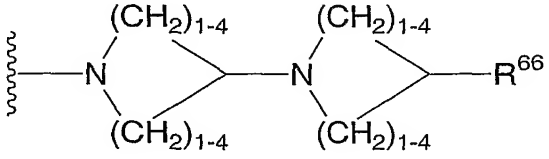
or a pharmaceutically acceptable salt thereof.

10. The compound according to Claim 1, wherein

R^2 is –NH–C(O)–$NR^{22}R^{23}$;

R^{23} is –C_{0-4}alkylaryl, wherein the aryl is substituted with –$(CH_2)_{0-4}$–R^{25}, or –C(O)–R^{25};

R^{25} is



;

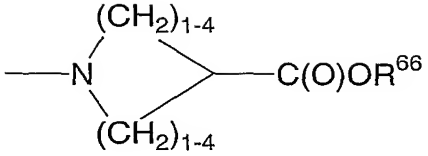
or a pharmaceutically acceptable salt thereof.

11. The compound according to Claim 1, wherein

R^2 is –NH–C(O)–$NR^{22}R^{23}$;

R^{23} is –C_{0-4}alkylaryl, wherein the aryl is substituted with –$(CH_2)_{0-4}$–R^{25}, or –C(O)–R^{25};

R^{25} is



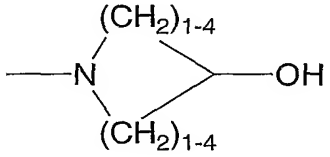
or a pharmaceutically acceptable salt thereof.

12. The compound according to Claim 1, wherein

R^2 is –NH–C(O)–$NR^{22}R^{23}$;

R^{23} is –C_{0-4}alkylaryl, wherein the aryl is substituted with –$(CH_2)_{0-4}$–R^{25}, or –C(O)–R^{25};

R^{25} is



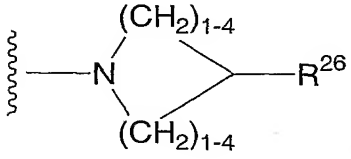
or a pharmaceutically acceptable salt thereof.

13. The compound according to Claim 1, wherein

R^2 is –NH–C(O)–$NR^{22}R^{23}$;

R^{23} is –C_{0-4}alkylaryl, wherein the aryl is substituted with –$(CH_2)_{0-4}$–R^{25}, or –C(O)–R^{25};

R^{25} is



; and

R^{26} is aryl, wherein the aryl is optionally substituted with 1-2 substituents, each substituent independently is C_{1-6}alkyl (optionally substituted with 1-9 independent halogens), C_{1-6}alkyloxy–, C_{1-6}alkylcarboxy–, C_{1-6}alkylamido–, OH, halogen, nitro, amino, or cyano;

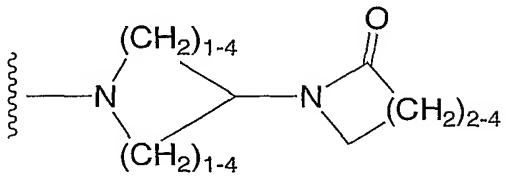
or a pharmaceutically acceptable salt thereof.

14. The compound according to Claim 1, wherein

R^2 is –NH–C(O)–$NR^{22}R^{23}$;

R^{23} is –C_{0-4}alkylaryl, wherein the aryl is substituted with –$(CH_2)_{0-4}$–R^{25}, or –C(O)–R^{25};

R^{25} is



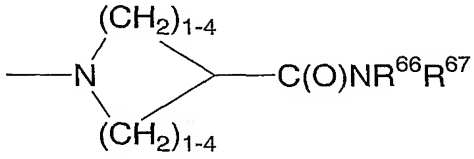
or a pharmaceutically acceptable salt thereof.

15. The compound according to Claim 1, wherein

R^2 is –NH–C(O)–$NR^{22}R^{23}$;

R^{23} is –C_{0-4}alkylaryl, wherein the aryl is substituted with –$(CH_2)_{0-4}$–R^{25}, or –C(O)–R^{25};

R^{25} is



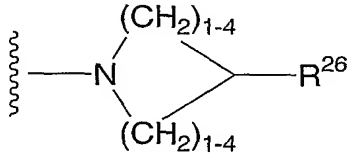
or a pharmaceutically acceptable salt thereof.

16. The compound according to Claim 1, wherein

R^2 is –NH–C(O)–$NR^{22}R^{23}$;

R^{23} is –C_{2-6}alkyl–R^{25};

R^{25} is



; and

R^{26} is aryl or heteroaryl, wherein the aryl or heteroaryl is optionally substituted with 1-2 substituents, each substituent independently is C_{1-6}alkyl

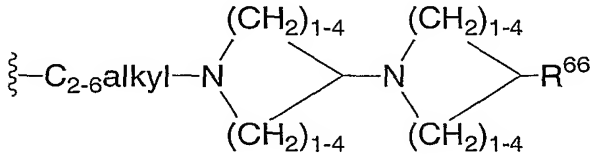
(optionally substituted with 1-9 independent halogens), C_{1-6}alkyloxy–, C_{1-6}alkylcarboxy–, C_{1-6}alkylamido–, OH, halogen, nitro, amino, or cyano;

or a pharmaceutically acceptable salt thereof.

17. The compound according to Claim 1, wherein

R^2 is –NH–C(O)–$NR^{22}R^{23}$;

R^{23} is –



or a pharmaceutically acceptable salt thereof.

18. The compound according to Claim 1, wherein

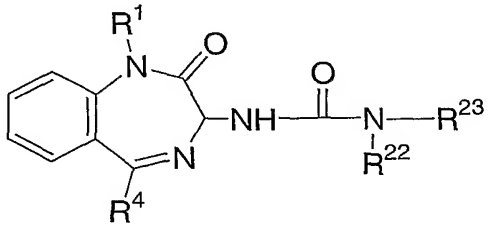
R^2 is –NH–C(O)–$NR^{22}R^{23}$;

R^{23} is –C_{0-4}alkylaryl, wherein the aryl is substituted with

;

or a pharmaceutically acceptable salt thereof.

19. The compound according to Claim 1, represented by



wherein:

R1	**R3**	**R^{23} (R^{22} = H unless otherwise noted)**
propyl	phenyl	4-[4-(pyridin-4-yl)piperazin-1-yl]phenyl
propyl	cyclohexyl	4-[4-(pyridin-3-yl)piperazin-1-yl]phenyl
propyl	cyclohexyl	2-[4-(pyridin-4-yl)piperazin-1-yl]phenyl
propyl	cyclohexyl	3-[4-(pyridin-4-yl)piperazin-1-yl]phenyl

R^1	R^3	R^{23} (R^{22} = H unless otherwise noted)
propyl	phenethyl	4-[4-(pyridin-4-yl)piperidin-1-yl]phenyl
propyl	phenethyl	3-bromo-4-[4-(3-bromopyridin-4-yl)piperazin-1-yl]phenyl
propyl	cyclohexyl	3-[(1,4'-bipiperidin-1'-yl)methyl]phenyl
propyl	cyclohexyl	3-[(1,4'-bipiperidin-1'-yl)carbonyl]phenyl
propyl	cyclohexyl	4-[(1,4'-bipiperidin-1'-yl)]benzyl
propyl	1-piperdinyl	4-[(1,4'-bipiperidin-1'-yl)]phenyl
allyl	cyclohexyl	4-[(1,4'-bipiperidin-1'-yl)]phenyl; R^{22} = allyl
isopropyl	phenyl	4-(4-carboxypiperidin-1-yl)phenyl
propyl	cyclohexyl	4-(4-carboxypiperidin-1-yl)phenyl
propyl	cyclohexyl	3-[(4-hydroxypiperidin-1-yl)methyl]phenyl
isopropyl	phenyl	4-(4-carboxamidopiperidin-1-yl)phenyl
propyl	cyclohexyl	3-(4-(4-fluorophenyl)piperidin-1-yl)propyl
propyl	cyclohexyl	3-(1,4'-bipiperidin-1'-yl)propyl
propyl	cyclohexyl	4-(1,4'-bipiperidin-1'-yl)butyl
propyl	cyclohexyl	4-(pyridin-4-ylethynyl)phenyl
propyl	cyclohexyl	2-(pyridin-4-ylethynyl)phenyl
propyl	cyclohexyl	3-(pyridin-4-ylethynyl)phenyl

or a pharmaceutically acceptable salt thereof.

20. The compound according to Claim 1, wherein

R^2 is –NH–C(O)–$NR^{22}R^{23}$;

R^{23} is 4-(4-pyridin-4-ylpiperazin-1-yl)phenyl; R^5 is H; R^4 is cyclohexyl and R^1 is propyl, cyclopropylmethyl, butyl, isobutyl, or 2,2,2-trifluoro-ethyl, or R^4 is phenyl and R^1 is isopropyl; or

R^{23} is 4-(1,4'-bipiperidin-1'-yl)phenyl; R^5 is H; and R^1 and R^4 are as follows:

R^1	R^4
Isopropyl	phenyl
Cyclopropylmethyl	Cyclohexyl
Methyl	phenyl

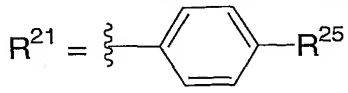
R^1	R^4
Propyl	Cyclohexyl
Propyl	isopropyl
H	cyclohexyl
Propyl	tert-butyl
Propyl	methyl
Propyl	2-phenylethyl
Butyl	cyclohexyl
Isobutyl	cyclohexyl
Propyl	4-tert-butylcyclohexyl
Propyl	3,5-dimethylcyclohexyl
2,2,2-trifluoroethyl	cyclohexyl
Propyl	4-methylphenyl
Propyl	3-butenyl
Propyl	butyl

or

R^{23} is 4-[4-(dimethylamino)piperidin-1-yl]phenyl; R^5 is H; R^4 is cyclohexyl and R^1 is propyl, cyclopropylmethyl, or benzyl, or R^4 is phenyl and R^1 is isopropyl, methyl or ethyl; or

R^{23} is 4-[[3-(dimethylamino)propyl](methyl)amino]phenyl; R^5 is H; R^1 is isopropyl and R^4 is phenyl, or R^1 is propyl and R^4 is isopropyl or cyclohexyl; or

R^{23} is 6-(1,4'-bipiperidin-1'-yl)pyridin-3-yl; R^4 is cyclohexyl; R^5 is H; and R^1 is propyl, cyclopropylmethyl, butyl or isobutyl; or



; R^5 is H, and R^1, R^4, and R^{25} are as follows:

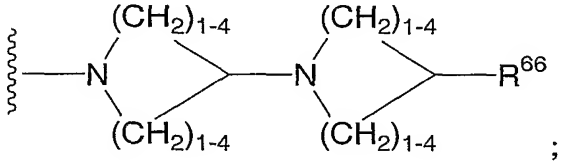
R^1	R^4	R^{25}
Isopropyl	Phenyl	4-(ethoxycarbonyl)piperidin-1-yl
Propyl	Isopropyl	4-pyrrolidin-1-ylpiperidin-1-yl
Propyl	Cyclohexyl	4-pyrrolidin-1-ylpiperidin-1-yl
Propyl	Cyclohexyl	4-hydroxypiperidin-1-yl
Propyl	Cyclohexyl	4-phenylpiperidin-1-yl

R^1	R^4	R^{25}
Propyl	Cyclohexyl	4-(ethoxycarbonyl)piperidin-1-yl
Propyl	Cyclohexyl	4-phenylpiperazin-1-yl
Propyl	Cyclohexyl	4-(2-oxopyrrolidin-1-yl)piperidin-1-yl
Propyl	Cyclohexyl	4-benzylpiperazin-1-yl
Propyl	Cyclohexyl	4-pyridin-2-ylpiperazin-1-yl

or a pharmaceutically acceptable salt thereof.

21. The compound according to Claim 1, wherein
R^2 is $-O-C(O)-NR^{22}R^{23}$;
or a pharmaceutically acceptable salt thereof.

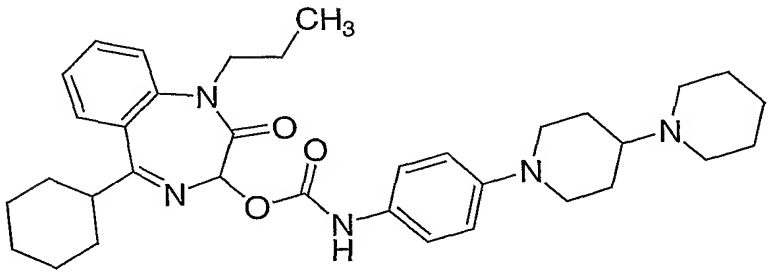
22. The compound according to Claim 21 wherein
R^{23} is $-C_{0-4}$alkylaryl, wherein the aryl is optionally substituted with 1-2 substituents, each substituent independently is $-(CH_2)_{0-4}-R^{25}$, or $-C(O)-R^{25}$;
R^{25} is



;

or a pharmaceutically acceptable salt thereof.

23. The compound according to Claim 21 represented by

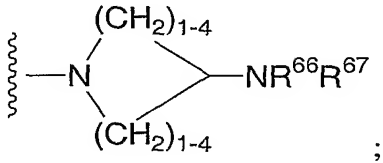


or a pharmaceutically acceptable salt thereof.

24. The compound according to Claim 1, wherein
R^2 is $-C_{1-3}alkyl-C(O)-NR^{22}R^{23}$;

or a pharmaceutically acceptable salt thereof.

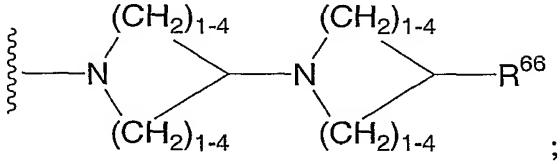
25. The compound according to Claim 24, wherein
R^{23} is $-C_{0-4}alkylaryl$, wherein the aryl is substituted with $-(CH_2)_{0-4}-R^{25}$, or $-C(O)-R^{25}$;
R^{25} is



;

or a pharmaceutically acceptable salt thereof.

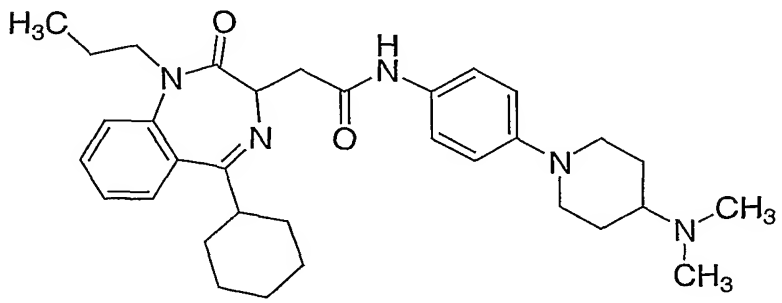
26. The compound according to Claim 24, wherein
R^{23} is $-C_{0-4}alkylaryl$, wherein the aryl is substituted with $-(CH_2)_{0-4}-R^{25}$, or $-C(O)-R^{25}$;
R^{25} is

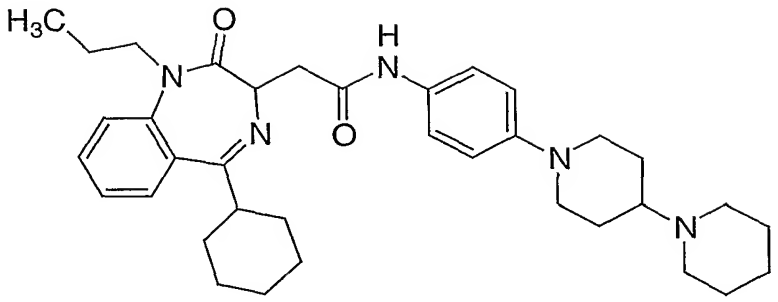


;

or a pharmaceutically acceptable salt thereof.

27. The compound according to Claim 24, represented by

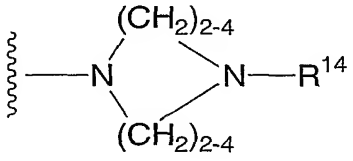




or a pharmaceutically acceptable salt thereof.

28. The compound according to Claim 1, wherein
R^1 is $-C_{1-7}$alkyl–C(O)-NH-R^{12};
or a pharmaceutically acceptable salt thereof.

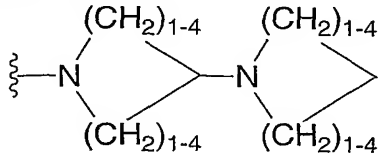
29. The compound according to Claim 28, wherein
R^{12} is aryl substituted with



; and

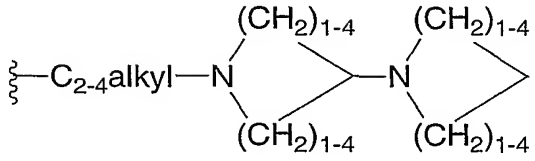
R^{14} is heteroaryl, wherein the aryl or heteroaryl is optionally substituted with 1-2 substituents, each substituent independently is C_{1-6}alkyl, C_{1-6}alkyloxy–, C_{1-6}alkylcarboxy–, C_{1-6}alkylamido–, OH, halogen, nitro, amino, or cyano;
or a pharmaceutically acceptable salt thereof.

30. The compound according to Claim 28, wherein
R^{12} is aryl substituted with



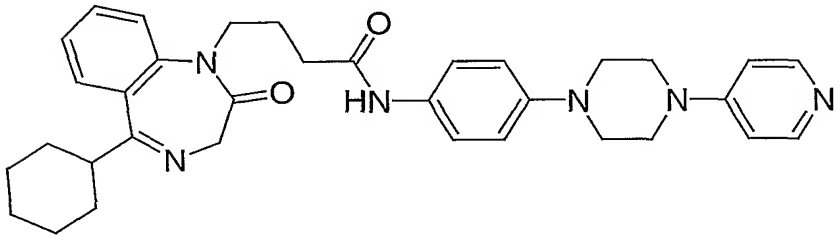
or a pharmaceutically acceptable salt thereof.

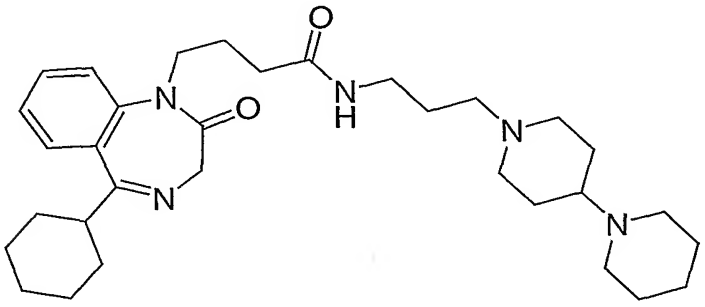
31. The compound according to Claim 28, wherein R^{12} is



or a pharmaceutically acceptable salt thereof.

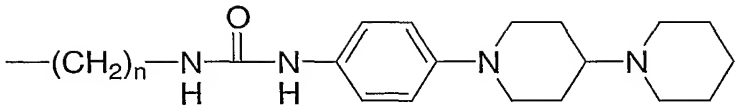
32. The compound according to Claim 28 represented by





or a pharmaceutically acceptable salt thereof.

33. The compound according to Claim 28, wherein R^{1} is



R^5 = H; and

n and R^4 is cyclohexyl and n is 1 to 5; or

n is 3 and R^4 is 2-phenylethyl, t-butyl or methyl;

or a pharmaceutically acceptable salt thereof.

34. The compound according to Claim 1 selected from

N-[4-(1,4'-bipiperidin-1'-yl)phenyl]-4-(5-cyclohexyl-2-oxo-2,3-dihydro-1H-1,4-benzodiazepin-1-yl)butanamide,

N-[2-oxo-5-(2-phenylethyl)-1-propyl-2,3-dihydro-1H-1,4-benzodiazepin-3-yl]-N'-[4-(4-pyridin-4-ylpiperazin-1-yl)phenyl]urea,

N-[4-(1,4'-bipiperidin-1'-yl)phenyl]-N'-(5-cyclohexyl-2-oxo-1-propyl-2,3-dihydro-1H-1,4-benzodiazepin-3-yl)urea, and

N-[4-(1,4'-bipiperidin-1'-yl)phenyl]-N'-[5-(4-methylphenyl)-2-oxo-1-propyl-2,3-dihydro-1H-1,4-benzodiazepin-3-yl]urea,

or a pharmaceutically acceptable salt thereof.

35. A pharmaceutical composition comprising a compound according to Claim 1 or a pharmaceutically acceptable salt thereof; and a pharmaceutically acceptable carrier.

36. A method of treatment or prevention of pain and inflammation comprising a step of administering, to a subject in need of such treatment or prevention, an effective amount of a compound according to Claim 1 or a pharmaceutically acceptable salt thereof.

37. A method of treatment of osteoarthritis, repetitive motion pain, dental pain, cancer pain, myofascial pain, muscular injury pain, fibromyalgia pain, perioperative pain comprising a step of administering, to a subject in need of such treatment, an effective amount of a compound according to Claim 1 or a pharmaceutically acceptable salt thereof.

38. A method of treatment or prevention of inflammatory pain caused by chronic obstructive pulmonary disease, asthma, inflammatory bowel disease, rhinitis, pancreatitis, cystitis (interstitial cystitis), uveitis, inflammatory skin disorders, rheumatoid arthritis, edema resulting from trauma associated with burns, sprains or fracture, postsurgical intervention, osteoarthritis, rheumatic disease, teno-synovitis, or gout comprising a step of administering, to a subject in need of such treatment or prevention, an effective amount of a compound according to Claim 1 or a pharmaceutically acceptable salt thereof.

39. A method of treatment or prevention of pain associated with angina, menstruation or cancer comprising a step of administering, to a subject in need of such treatment or prevention, an effective amount of a compound according to Claim 1 or a pharmaceutically acceptable salt thereof.

40. A method of treatment of diabetic vasculopathy, post capillary resistance, diabetic symptoms associated with insulitis, psoriasis, eczema, spasms of the gastrointestinal tract or uterus, Crohn's disease, ulcerative colitis, or pancreatitis comprising a step of administering, to a subject in need of such treatment, an effective amount of a compound according to Claim 1 or a pharmaceutically acceptable salt thereof.

41. A method of treatment or prevention of pain caused by pneumoconiosis, including aluminosis, anthracosis, asbestosis, chalicosis, ptilosis, siderosis, silicosis, tabacosis, byssinosis, adult respiratory distress syndrome, bronchitis, allergic rhinitis, vasomotor rhinitis, liver disease, multiple sclerosis, atherosclerosis, Alzheimer's disease, septic shock, cerebral edema, headache, migraine, closed head trauma, irritable bowel syndrome, or nephritis comprising a step of administering, to a subject in need of such treatment or prevention of pain, an effective amount of a compound according to Claim 1 or a pharmaceutically acceptable salt thereof.

42. A compound selected from the group:

N-(1-methyl-5-phenyl-2-oxo-2,3-dihydro-1H-1,4-benzodiazepin-3-yl)-4-(n-pentyl)benzamide;

N-(1-methyl-5-(2-fluorophenyl)-2-oxo-2,3-dihydro-1H-1,4-benzodiazepin-3-yl)-4-(n-pentyl)benzamide;

N-(1-isopropyl-5-phenyl-2-oxo-2,3-dihydro-1H-1,4-benzodiazepin-3-yl)-3-bromobenzamide;

N-(1-isopropyl-5-phenyl-2-oxo-2,3-dihydro-1H-1,4-benzodiazepin-3-yl)-3-(trifluoromethyl)benzeneacetamide;

N-(5-cyclohexyl-2-oxo-2,3-dihydro-1H-1,4-benzodiazepin-3-yl)-2-(phenoxy)benzeneacetamide;

N-(5-(2-flurophenyl)-2-oxo-2,3-dihydro-1H-1,4-benzodiazepin-3-yl)-3-methyl-2-indencarboxamide;

N-(5-(2-fluorophenyl)-2-oxo-2,3-dihydro-1H-1,4-benzodiazepin-3-yl)-benzamide;

N-(1-methyl-5-phenyl-2-oxo-2,3-dihydro-1H-1,4-benzodiazepin-3-yl)-cyclohexanecarboxamide;

N-(1-propyl-5-cyclohexyl-2-oxo-2,3-dihydro-1H-1,4-benzodiazepin-3-yl)-4-(dimethylamino)benzamide;

N-(1-propyl-5-cyclohexyl-2-oxo-2,3-dihydro-1H-1,4-benzodiazepin-3-yl)-1H-5-indolecarboxamide;

N-[2-oxo-5-phenyl-1-isopropyl-2,3-dihydro-1H-1,4-benzodiazepin-3-yl]-N'-[4-((3-(dimethylamino)propyl(methyl)amino)phenyl]urea;

N-[2-oxo-5-isopropyl-1-propyl-2,3-dihydro-1H-1,4-benzodiazepin-3-yl]-N'-[4-((3-(dimethylamino)propyl(methyl)amino)phenyl]urea;

N-[2-oxo-5-cyclohexyl-1-propyl-2,3-dihydro-1H-1,4-benzodiazepin-3-yl]-N'-[4-((3-(dimethylamino)propyl(methyl)amino)phenyl]urea;

N-[2-oxo-5-cyclohexyl-1-propyl-2,3-dihydro-1H-1,4-benzodiazepin-3-yl]-N'-[4-(2-(piperidin-1-yl)ethoxy)phenyl]urea;

N-[2-oxo-5-phenyl-1-ethyl-2,3-dihydro-1H-1,4-benzodiazepin-3-yl]-N'-(3-methoxyphenyl)urea;

N-[2-oxo-5-isopropyl-1-propyl-2,3-dihydro-1H-1,4-benzodiazepin-3-yl]-N'-[4-(morpholin-4-yl)phenyl]urea;

N-[2-oxo-5-cyclohexyl-1-propyl-2,3-dihydro-1H-1,4-benzodiazepin-3-yl]-N'-[4-(morpholin-4-yl)phenyl]urea;

N-[2-oxo-5-cyclohexyl-1-propyl-2,3-dihydro-1H-1,4-benzodiazepin-3-yl]-N'-[4-(piperidin-1-yl)phenyl]urea;

N-[2-oxo-5-cyclohexyl-1-propyl-2,3-dihydro-1H-1,4-benzodiazepin-3-yl]-N'-(3-pyridyl)urea;

Benzyl 5-tert-butyl-1-isobutyl-2-oxo-2,3-dihydro-1H-1,4-benzodiazepin-3-ylcarbamate;

N-[5-(4-methylpiperazin-1-yl)-2-oxo-1-propyl-2,3-dihydro-1H-1,4-benzodiazepin-3-yl]-N'-(5-methyl-1,3,4-thiadiazol-2-yl)urea; and

N-(5-azepan-1-yl-1-methyl-2-oxo-2,3-dihydro-1H-1,4-benzodiazepin-3-yl)-4-phenylbutanamide;

or a pharmaceutically acceptable salt thereof.